UPSTATE
MEDICAL UNIVERSITY

Therapeutic Use of Mechanical Ventilation: Can We Change the Way We Manage the Patient?

2014 Suncoast Pulmonary Symposium
Hyatt Regency Coconut Point Resort
Bonita Springs, Florida
September 10-12, 2014

Gary F. Nieman

Associate Professor

Department of Surgery

Director,

Cardiopulmonary and Critical Care Laboratory

SUNY Upstate Medical University

Syracuse, NY

Niemang@upstate.edu

UPSTATE
MEDICAL UNIVERSITY

Why is it Important to Prevent ARDS?

- Once established ARDS is very difficult to treat
  - Almost all clinical trials a failure (MacIntyre & Brower)
  - Low Vt only reduced ARDS moderately (ARDSnet)
  - Mortality of ARDS still 30-60% (Shari & Herridge)
  - Mortality is higher than Breast Cancer (Rubenfeld)
  - Even with Low Vt mortality still >40% (Villar ALIEN Study)

- Patients that develop established-ARDS often develop chronic lung and brain injury

UPSTATE
MEDICAL UNIVERSITY

Thirty years of clinical trials in acute respiratory distress syndrome

Robert C. McIntyre Jr, MD; Edward J. Pulido, MD; Denis D. Bensard, MD; Brian D. Shames, MD; Edward Abraham, MD, FCCM

(Crit Care Med 2000; 28:3314–3331)

UPSTATE MEDICAL UNIVERSITY

McIntyre *Crit Care Med*, 2000

Established-ARDS: Difficult to Treat

Table 2: ARDS Treatments, Evidence & Recommendations Systematically Reviewed	Adapted from Ware et. al [1] and Cepovka et al [2]	
Treatment Modality	**Evidence Level**	**Recommendation Grade**
Ventilatory		
-Low Tidal Volume	1 & 2	B
-Open Lung	2	B
-Inverse Ratio	3 & 4	D
-Liquid Ventilation	4	E
Extracorporeal Life Support	Level 1 & 2 *Against*	Not Recommended
Prone Positioning	3	D
Restrictive Fluid Management	2	C
	3	C
	Level 1 *Against*	Not Recommended
-Almitrine	3	C
-Prostacyclin	3	C
	ainst	Not Recommended
-Ketoconazole	Level 1 *Against*	Not Recommended
-Ibuprofen	Level 2 Mixed Results	Not Recommended At Any Level
-Corticosteroid	2	C
ysteine	Level 2 Mixed Results	Not Recommended At Any Level

ARDS: 14

The Good Guys: 1

Ouch..

UPSTATE MEDICAL UNIVERSITY

Established-ARDS: Difficult to Treat

TABLE 1. SELECTED RANDOMIZED CONTROLLED CLINICAL TRIALS IN ACUTE LUNG INJURY AND THE ACUTE RESPIRATORY DISTRESS SYNDROME*

	Year	No. Patients	Intervention	Clinical Outcome Result*
Surfactant trials				
Weg (27)	1994	51	Exosurf—aerosolized	NSD
Anzueto (11)	[illegible]	725	Exosurf—aerosolized	NSD
Gregory (14)	1997	59	Bovine surfactant—endotracheal instillation	NSD
Spragg (13)	2004	448	Protein C surfactant—endotracheal instillation	NSD
Kesecioglu (12)	2009	418	HL 10 surfactant—endotracheal instillation	NSD
Spragg (1)	2011	843	Protein C surfactant—endotracheal instillation	NSD
Other trials				
Zapol (18)	1979	90	ECMO	NSD
Amato (2)	1998	53	Lower tidal volume + higher PEEP	[illegible]otective approach better
Stewart (28)†	1998	120	Lower tidal volume/inspiratory pressure	NSD
Brochard (29)	1998	116	Lower tidal volume/plateau pressure	NSD
Brower (30)	1999	52	Lower tidal volume/plateau pressure	NSD
Abraham (17)	1999	350	Prostaglandin E1	NSD
ARDS Network/Steinberg (31)	2000	234	Ketoconazole	NSD
ARDS Network/Brower (3)	2000	861	Lower tidal volume/plateau pressure	[illegible]dal volume better
Gattinoni (32)	2001	304	Prone position	NSD
ARDS Network/Abraham (19)	2002	235	Lisofylline	NSD
Derdak (33)	2002	148	High frequency oscillatory ventilation	NSD
Taylor (16)	2004	385	Inhaled nitric oxide	NSD
ARDS Network/Brower (34)	2004	549	Higher PEEP	NSD
Kacmarek (35)	2006	311	Partial Liquid Ventilation	NSD
Mancebo (36)	2006	136	Prone positioning	NSD
ARDS Network/Steinberg (37)	2006	180	Methylprednisolone for persistent ARDS	NSD
ARDS Network/Wiedemann (38)	2006	1000	Fluid-conservative hemodynamic strategy	NSD‡
ARDS Network/Wheeler (39)	2006	1000	Pulmonary artery vs central venous catheter	NSD
Villar (4)	2006	95	Lower tidal volume + higher PEEP	Lung-protective approach better
Meduri (8)	2007	91	Methylprednisolone for early ARDS	[illegible]rednisolone better
Mercat (40)	2008	767	Higher PEEP	NSD
Meade (41)	2008	983	Higher PEEP	NSD
Taccone (42)	2009	342	Prone positioning	NSD
Peek (9)	[illegible]	180	Transfer to ECMO-capable center	Transfer better
Papazian (10)	2010	340	Neuromuscular blockade	Neuromuscular blockade better

Definition of abbreviations: ALI = acute lung injury; ARDS = acute respiratory distress syndrome; ECMO = extracorporeal membrane oxygenation; NSD = not significantly different PEEP = positive end-expiratory pressure.

Included trials enrolled at least 50 patients. Some trials with more than 50 patients were not included because they were pilot studies for subsequent trials.

* Results of primary outcome variable analysis.

† Patients at risk for ALI.

‡ Ventilator-free days (secondary outcome variable) was significantly greater in the fluid-conservative group.

Brower RG, *Am J Resp Crit Care Med*, 2011

UPSTATE
MEDICAL UNIVERSITY

Recently Failed Trials

Randomized, Placebo-controlled Clinical Trial of an Aerosolized β_2-Agonist for Treatment of Acute Lung Injury

The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network

Am J Respir Crit Care Med Vol 184. pp 561–568, 2011

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Preclinical studies and one clinical trial suggested that β_2-agonist therapy could reduce pulmonary edema in acute lung injury. However, the potential value of aerosolized β_2-agonist therapy for treatment of acute lung injury has not been tested previously in a phase III, randomized clinical trial.

What This Study Adds to the Field

The results of this randomized double-blind clinical trial demonstrate that aerosolized β_2-agonist therapy with albuterol did not improve clinical outcomes in patients with acute lung injury.

UPSTATE
MEDICAL UNIVERSITY

Recently Failed Trials

Recombinant Surfactant Protein C–based Surfactant for Patients with Severe Direct Lung Injury

Roger G. Spragg[1*], Friedemann J. H. Taut[2*], James F. Lewis[3], Peter Schenk[4], Clemens Ruppert[5], Nathan Dean[6], Kenneth Krell[7], Andreas Karabinis[8], and Andreas Günther[5]

Am J Respir Crit Care Med Vol 183. pp 1055–1061, 2011

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Prior studies have suggested that treatment with exogenous surfactant of patients with severe direct lung injury may be beneficial.

What This Study Adds to the Field

In this prospective, blinded, randomized study of 843 patients, delivery of a recombinant surfactant protein C–based surfactant provided no benefit to patients with severe direct lung injury.

UPSTATE
MEDICAL UNIVERSITY

Recently Failed Trials

The NEW ENGLAND JOURNAL of MEDICINE

2013

ORIGINAL ARTICLE

High-Frequency Oscillation in Early Acute Respiratory Distress Syndrome

Niall D. Ferguson, M.D., Deborah J. Cook, M.D., Gordon H. Guyatt, M.D.,

CONCLUSIONS

In adults with moderate-to-severe ARDS, early application of HFOV, as compared with a ventilation strategy of low tidal volume and high positive end-expiratory pressure, does not reduce, and may increase, in-hospital mortality. (Funded by the Canadian

UPSTATE
MEDICAL UNIVERSITY

Villar J, Curr Opin Crit Care 2014;20:3-9

No Reduction in ARDS Mortality since 1998

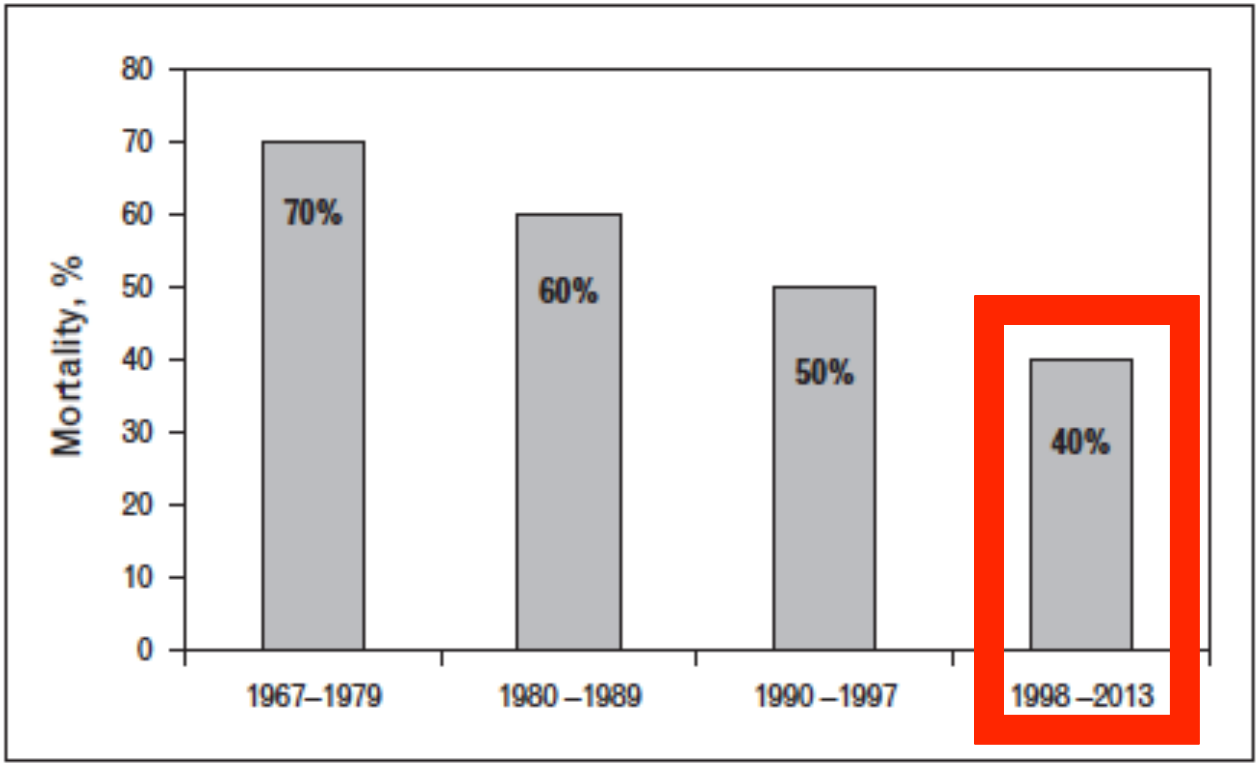


FIGURE 1. Schematic representation of average reported mortality in observational and randomized controlled trials in adult patients with acute respiratory distress syndrome since 1967. Data have been compiled from [6▪▪,11,12▪,26,27▪].

UPSTATE
MEDICAL UNIVERSITY

To Prevent ARDS we must Understand the Pathogenesis

- What is the role of mechanical ventilation in the development of *Established-ARDS*?
- Is there a 'treatment window' in the hospital during which ARDS can be treated?
- What is the progressive pulmonary pathophysiology as *EALI* evolves into *Established-ARDS* ?
- What kind of mechanical breath is necessary to prevent ARDS?

UPSTATE
MEDICAL UNIVERSITY

To Prevent ARDS we must Understand the Pathogenesis

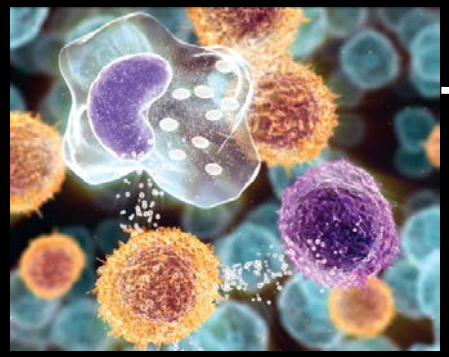
- What is the role of mechanical ventilation in the development of *Established-ARDS*?
- Is there a 'treatment window' in the hospital during which ARDS can be treated?
- What is the progressive pulmonary pathophysiology as *EALI* evolves into *Established-ARDS* ?
- What kind of mechanical breath is necessary to prevent ARDS?

UPSTATE
MEDICAL UNIVERSITY

Early Lung Inflammation

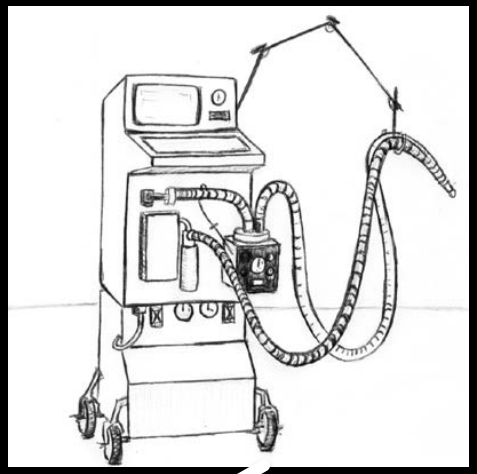
Systemic Inflammation

T/HS/S

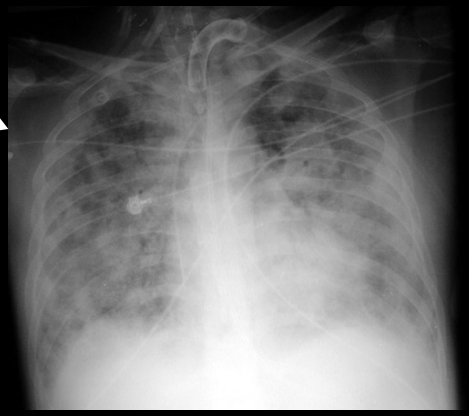


+

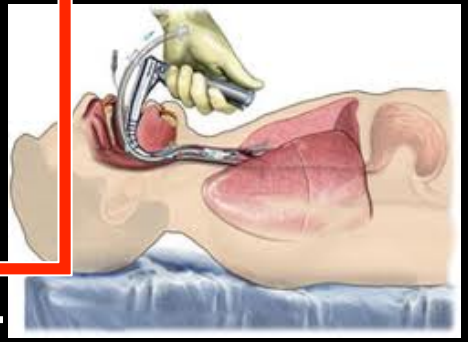
VILI



ARDS



Intubation



UPSTATE
MEDICAL UNIVERSITY

Is acute respiratory distress syndrome an iatrogenic disease?

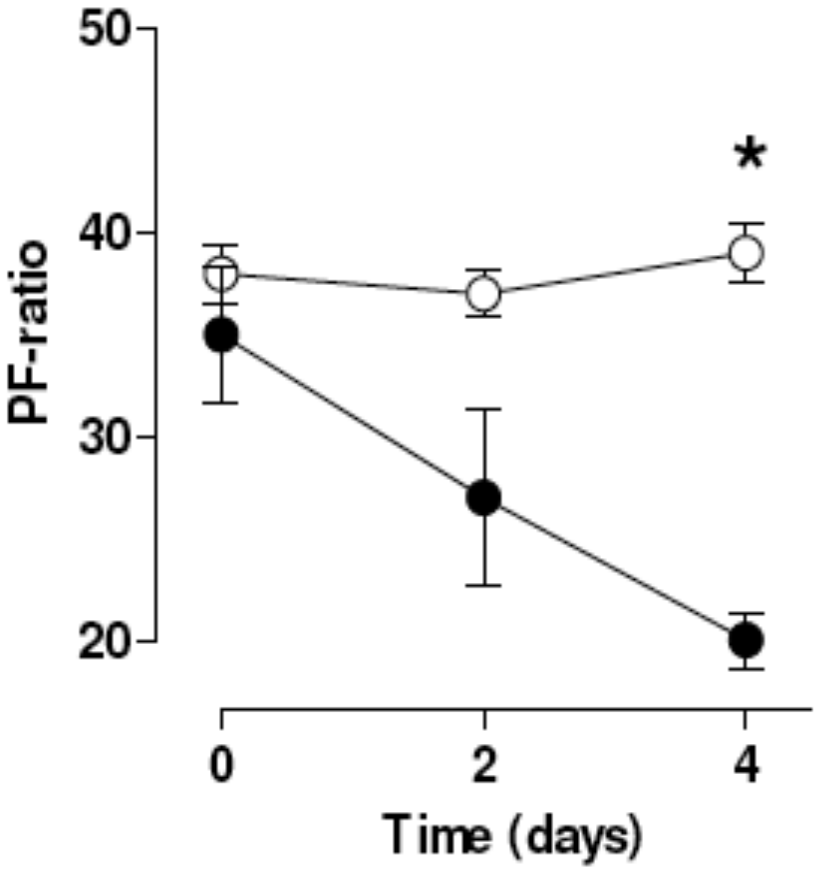
Jesús Villar[1,2,3] and Arthur S Slutsky[*3,4,5]

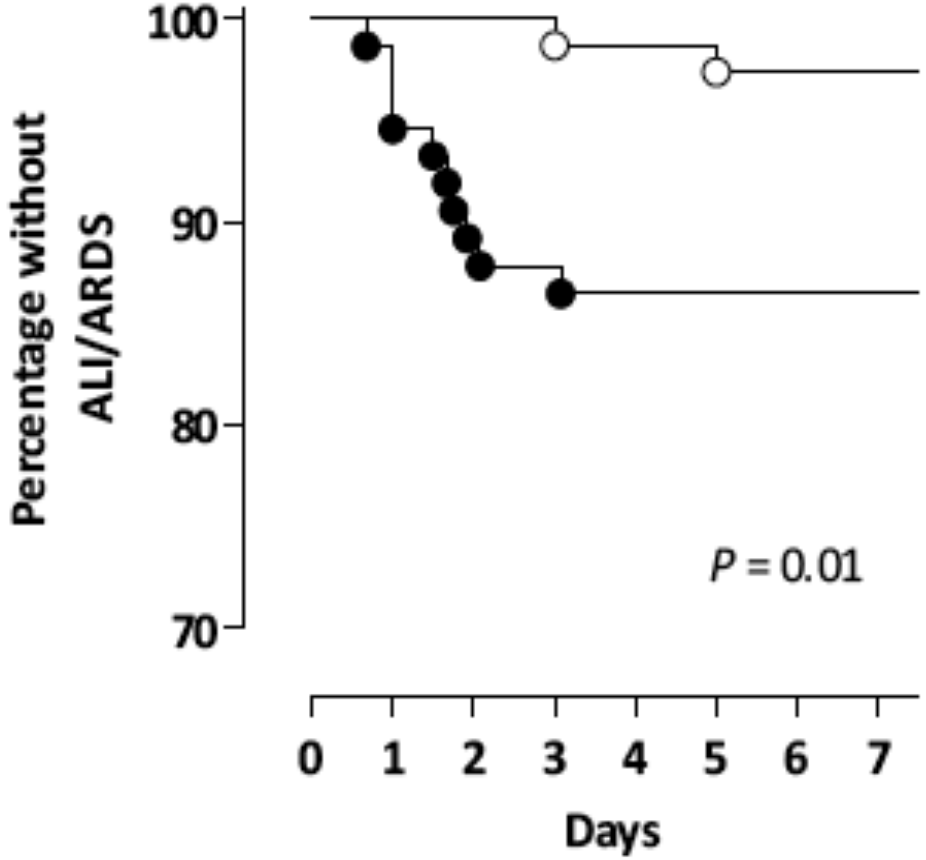
Critical Care 2010, 14:120

- "..should we begin to consider that ALI/ARDS is a consequence of our efforts rather than progression of the underlying disease?"
- "..injurious ventilation strategies have been shown to cause all of the pathology associated with ALI/ARDS."
- "..ALI/ARDS is largely a 'man-made' syndrome."
- "..ALI/ARDS is no longer a syndrome that must be treated, but is a syndrome that should be prevented."

UPSTATE
MEDICAL UNIVERSITY

Improper Ventilation in 'Normal' Lungs Drives ARDS.





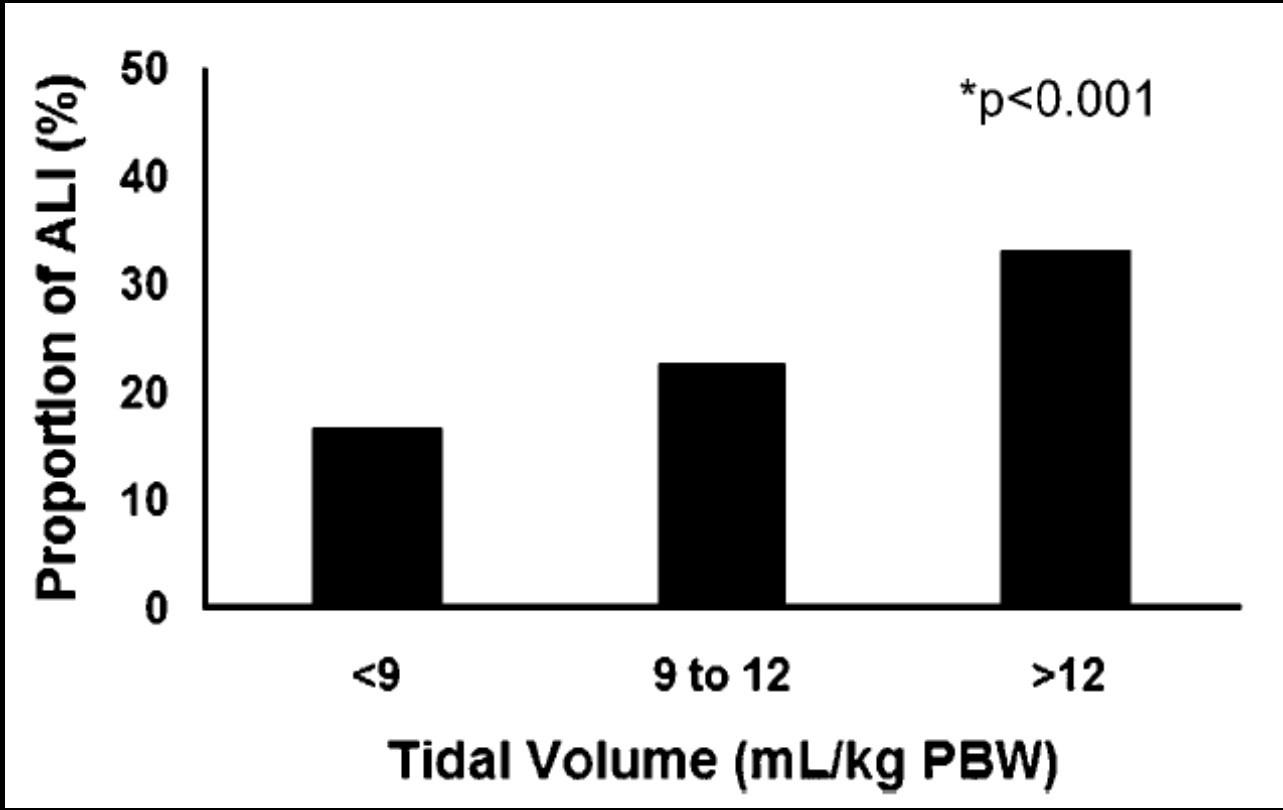
UPSTATE
MEDICAL UNIVERSITY

Ventilator-associated lung injury in patients without acute lung injury at the onset of mechanical ventilation*

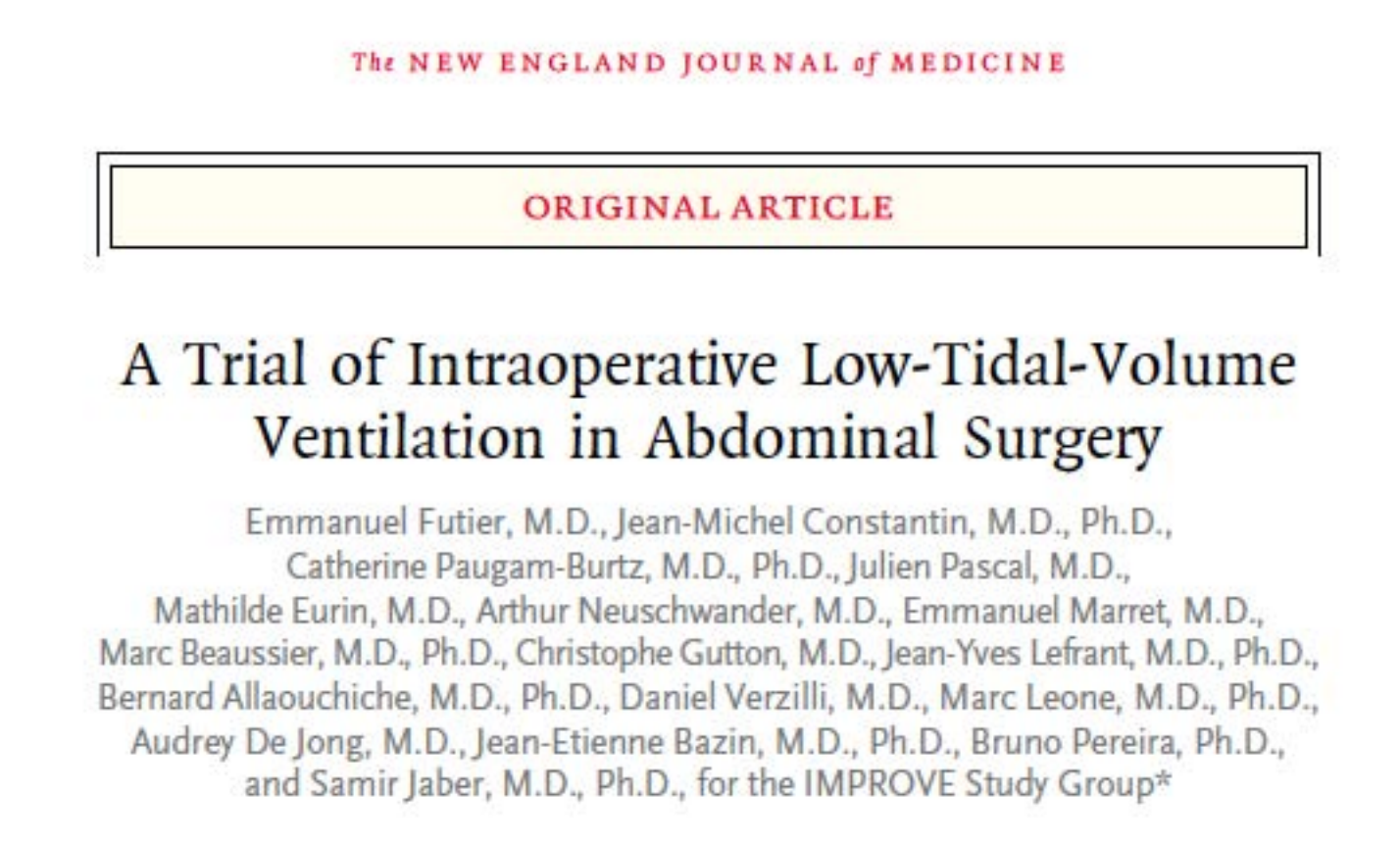
Ognjen Gajic, MD; Saqib I. Dara, MD; Jose L. Mendez, MD; Adebola O. Adesanya, MD; Emir Festic, MD; Sean M. Caples, MD; Rimki Rana, MD; Jennifer L. St. Sauver, PhD; James F. Lymp, PhD; Bekele Afessa, MD; Rolf D. Hubmayr, MD

Crit Care Med 2004

Patients in the ICU *without ALI* placed on multiple Vt's



UPSTATE
MEDICAL UNIVERSITY



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Trial of Intraoperative Low-Tidal-Volume Ventilation in Abdominal Surgery

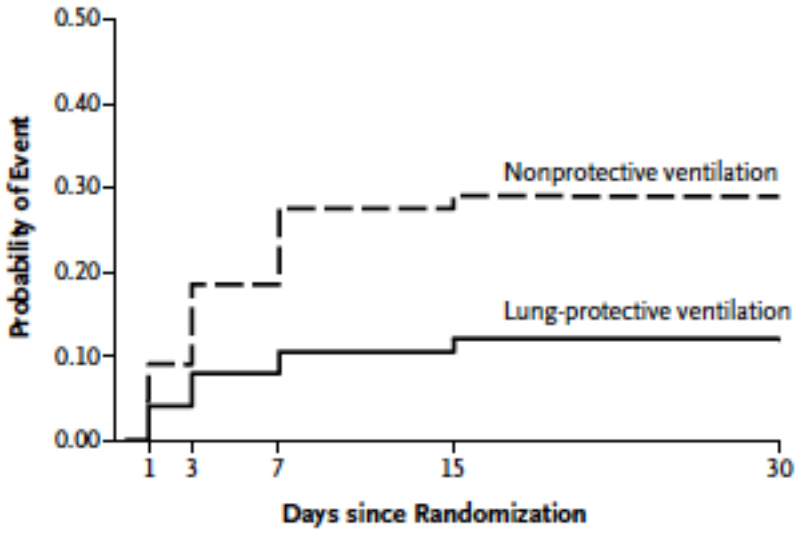
Emmanuel Futier, M.D., Jean-Michel Constantin, M.D., Ph.D., Catherine Paugam-Burtz, M.D., Ph.D., Julien Pascal, M.D., Mathilde Eurin, M.D., Arthur Neuschwander, M.D., Emmanuel Marret, M.D., Marc Beaussier, M.D., Ph.D., Christophe Gutton, M.D., Jean-Yves Lefrant, M.D., Ph.D., Bernard Allaouchiche, M.D., Ph.D., Daniel Verzilli, M.D., Marc Leone, M.D., Ph.D., Audrey De Jong, M.D., Jean-Etienne Bazin, M.D., Ph.D., Bruno Pereira, Ph.D., and Samir Jaber, M.D., Ph.D., for the IMPROVE Study Group*

N ENGL J MED 369;5 NEJM.ORG AUGUST 1, 2013

Non-protective Ventilation = Vt 10-12cc/kg 0 PEEP
Lung-protective Ventilation = Vt 6-8cc/kg, 6-8 PEEP + RM

UPSTATE
MEDICAL UNIVERSITY

Reduced Major Complications

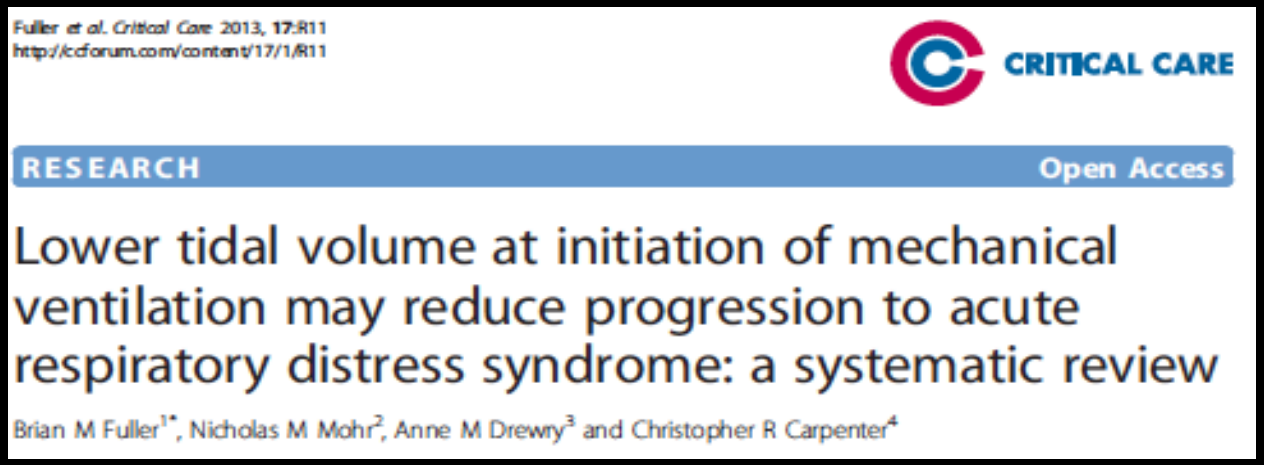


No. at Risk						
Nonprotective ventilation	200	182	163	145	142	142
Lung-protective ventilation	200	192	184	179	176	175

Figure 2. Kaplan–Meier Estimates of the Probability of the Composite Primary Outcome.

Data for the Kaplan–Meier estimates of the probability of the composite primary outcome of major pulmonary or extrapulmonary complications were censored at 30 days after surgery. Major pulmonary complications included pneumonia or the need for invasive or noninvasive ventilation for acute respiratory failure. Major extrapulmonary complications were sepsis, severe sepsis, septic shock, and death. $P<0.001$ by the log-rank test for the between-group difference in the probability of the primary outcome.

UPSTATE
MEDICAL UNIVERSITY



- Key Messages
  - Higher Vt are causal in the development of ARDS
  - ARDS occurs early in the course of mechanical ventilation suggesting that ARDS-prevention trials should occur early, such as in the emergency department
  - The development of ARDS is associated with significant increases in mortality and morbidity, suggesting that ARDS-prevention trials are needed

UPSTATE
MEDICAL UNIVERSITY

To Prevent ARDS we must Understand the Pathogenesis

- What is the role of mechanical ventilation in the development of *Established-ARDS*?
- Conclusion: MV plays a major role in ARDS pathogenesis

- Is there a 'treatment window' in the hospital during which ARDS can be treated?

- What is the progressive pulmonary pathophysiology as *EALI* evolves into *Established-ARDS* ?

- What are the key pathologic components that comprise pre-ARDS pathophysiology?

UPSTATE
MEDICAL UNIVERSITY

To Prevent ARDS we must Understand the Pathogenesis

- What is the role of mechanical ventilation in the development of *Established-ARDS*?
- Conclusion: MV plays a major role in ARDS pathogenesis

- Is there a 'treatment window' in the hospital during which ARDS can be treated?

- What is the progressive pulmonary pathophysiology as *EALI* evolves into *Established-ARDS* ?

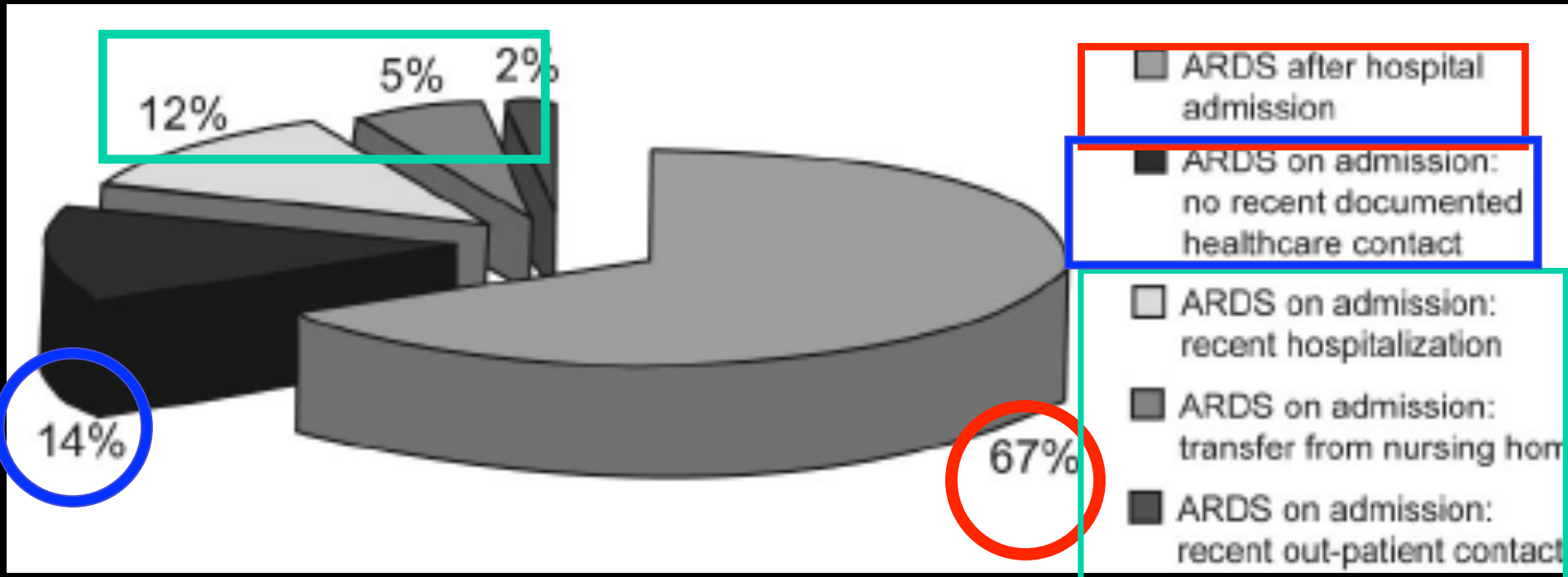
- What kind of mechanical breath is necessary to prevent ARDS?

UPSTATE
MEDICAL UNIVERSITY

Timing of the Onset of Acute Respiratory Distress Syndrome: A Population-Based Study

Giath Shari MD, Marija Kojicic MD, Guangxi Li MD, Rodrigo Cartin-Ceba MD, Cesar Trillo Alvarez MD, Rahul Kashyap MBBS, Yue Dong MD, Jaise T Poulose MBBS, Vitaly Herasevich MD, Javier A Cabello Garza MD, and Ognjen Gajic MD

Respir Care 2011;56(5):576–582.



86% of ARDS Develops in a Hospital

UPSTATE
MEDICAL UNIVERSITY

To Prevent ARDS we must Understand the Pathogenesis

- What is the role of mechanical ventilation in the development of *Established-ARDS*?

- Is there a 'treatment window' in the hospital during which ARDS can be treated?
  - Most ARDS develops in the hospital so there is an opportunity to prevent

- What is the progressive pulmonary pathophysiology as *EALI* evolves into *Established-ARDS* ?

- What are the key pathologic components that comprise pre-ARDS pathophysiology?

UPSTATE
MEDICAL UNIVERSITY

To Prevent ARDS we must Understand the Pathogenesis

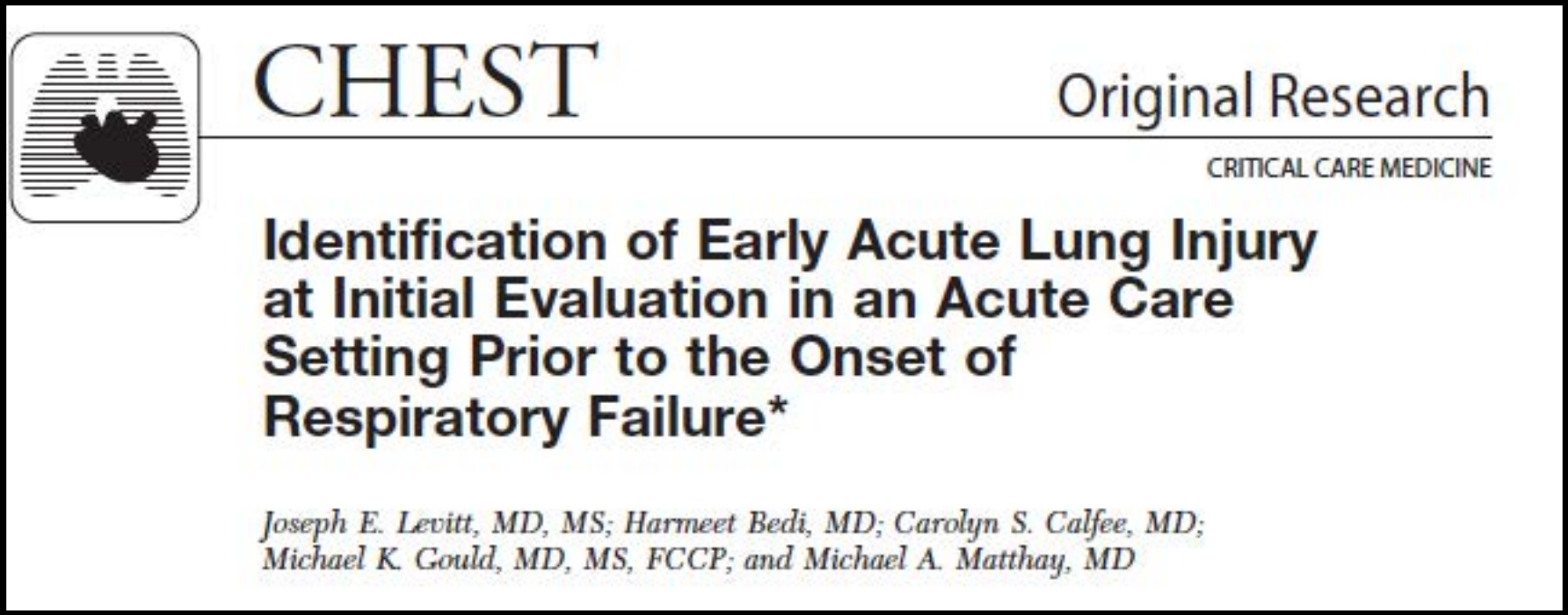
- What is the role of mechanical ventilation in the development of *Established-ARDS*?

- Is there a 'treatment window' in the hospital during which ARDS can be treated?
  - Most ARDS develops in the hospital so there is an opportunity to prevent

- What is the progressive pulmonary pathophysiology as *EALI* evolves into *Established-ARDS* ?

- What are the key pathologic components that comprise pre-ARDS pathophysiology?

UPSTATE
MEDICAL UNIVERSITY



CHEST Original Research

CRITICAL CARE MEDICINE

Identification of Early Acute Lung Injury at Initial Evaluation in an Acute Care Setting Prior to the Onset of Respiratory Failure*

Joseph E. Levitt, MD, MS; Harmeet Bedi, MD; Carolyn S. Calfee, MD; Michael K. Gould, MD, MS, FCCP; and Michael A. Matthay, MD

(CHEST 2009; 135:936–943)

Early Acute Lung Injury (EALI): ***Before*** the patient is placed on MV

UPSTATE
MEDICAL UNIVERSITY

Early Acute Lung Injury (EALI) Criteria

- Admission with Bilateral infiltrates on CXR
- Initial O_2 requirement of >2L/min
- Strong predictor of patient progressing to ALI
  - 73% sensitivity
  - 79% specificity

(CHEST 2009; 135:936–943)

UPSTATE
MEDICAL UNIVERSITY

ARDS Staging

- Once the patient progresses from EALI to ALI and is placed on mechanical ventilation the lung progresses through an additional 3-Stages of progressively increasing pathology

UPSTATE
MEDICAL UNIVERSITY

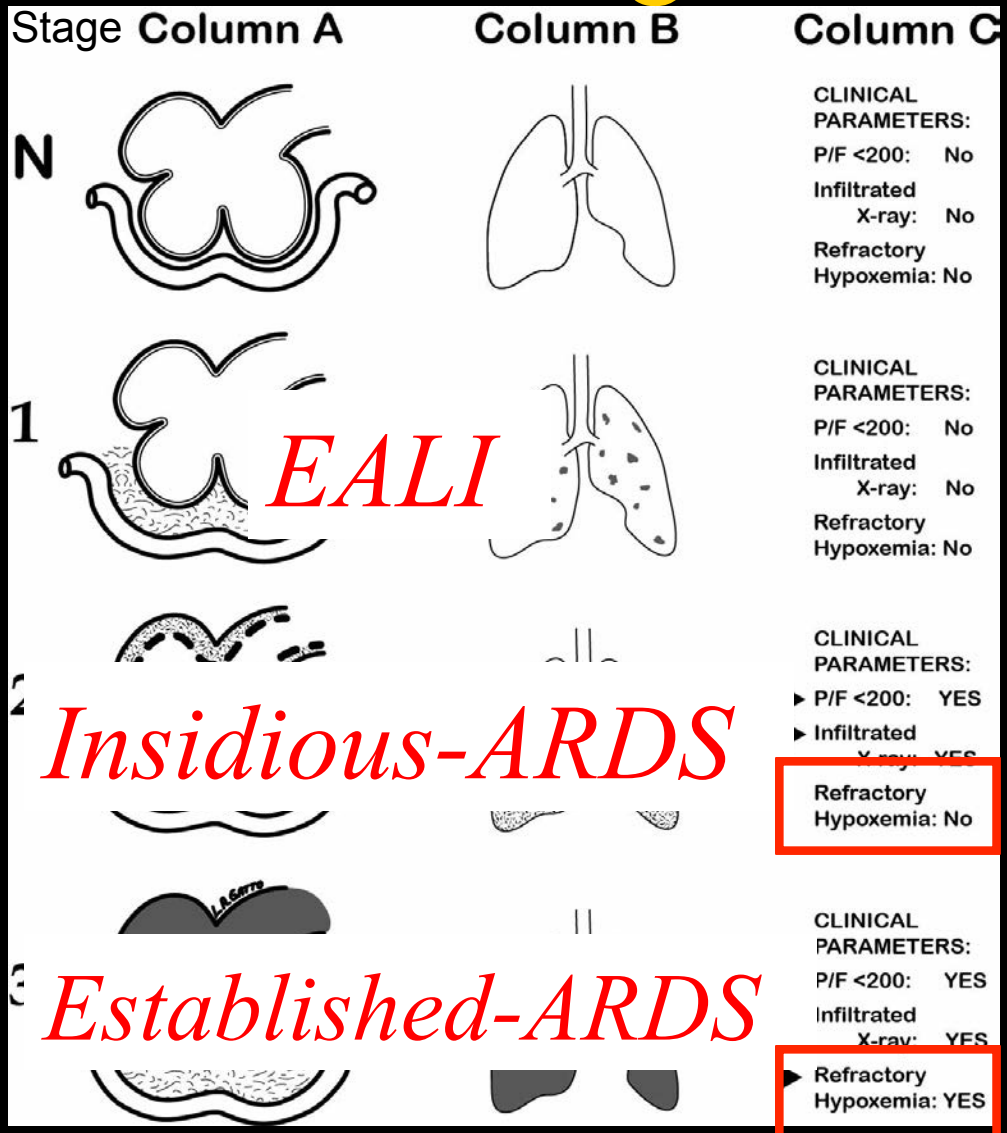
Acute Respiratory Distress Syndrome
The Berlin Definition

The ARDS Definition Task Force*
JAMA. 2012;307(23):2526-2533
Published online May 21, 2012. doi:10.1001/jama.2012.5669

- Degrees of *ARDS*
  - Mild ARDS: P/F≤300 with PEEP≥5
  - Moderate ARDS: P/F≤200 with PEEP≥5
  - Severe ARDS: P/F≤ 100 with PEEP≥5

UPSTATE
MEDICAL UNIVERSITY

ARDS Pathogenesis



Roy et al *J Trauma Acute Care Surg.* 2012,73: 391

UPSTATE
MEDICAL UNIVERSITY

What is *Insidious-ARDS* and is there proof that it exists?

Insidious-ARDS is an early stage of ARDS that is treatable and presents with the identical clinical *symptoms as does Established-ARDS, however, with a maneuver such as a* ***FiO_2-PEEP Trial*** oxygenation dramatically improves and the patient no longer meets AECC defined ARDS

UPSTATE
MEDICAL UNIVERSITY

Intensive Care Med (2004) 30:1111–1116
DOI 10.1007/s00134-004-2163-2

ORIGINAL

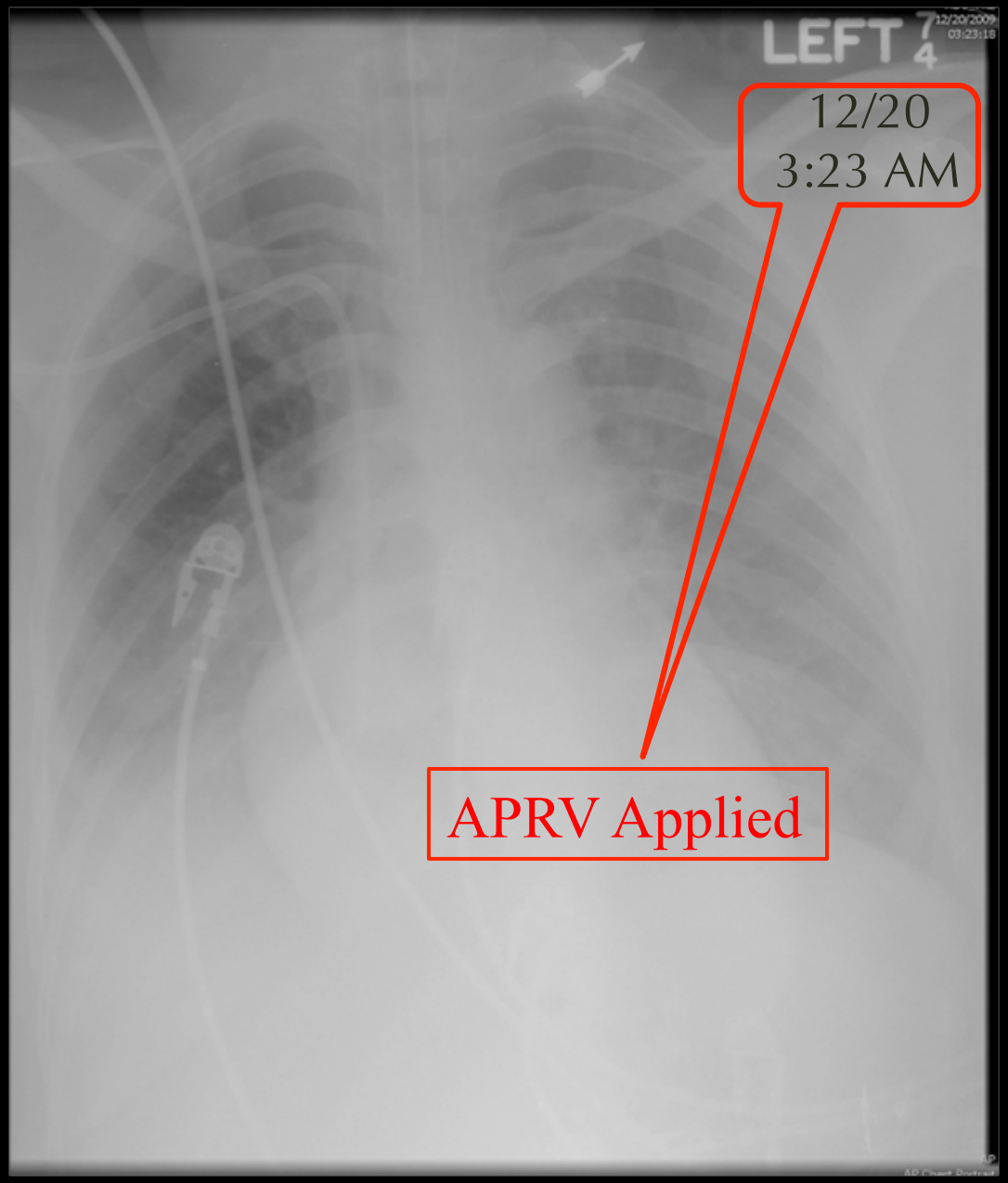
Niall D. Ferguson
Robert M. Kacmarek
Jean-Daniel Chiche
Jeffrey M. Singh
David C. Hallett
Sangeeta Mehta
Thomas E. Stewart

Screening of ARDS patients using standardized ventilator settings: influence on enrollment in a clinical trial

- Observation: Patients with AECC defined ARDS have a P/F <200 *regardless of ventilator settings*
- Intervention: Screening these patients with standardized ventilator settings would identify *Persistent-ARDS*
  - Vt 7-8 ml/kg
  - PEEP 10 cmH_2O
  - FiO_2 100%
- Results: *Persistent-ARDS* 42%; *Transient-ARDS* 59%
- Conclusion: This study supports the concept of a slow progressive pathogenesis for ARDS and suggests that preemptive application with the correct *Mechanical Breath* may be able to block disease progression

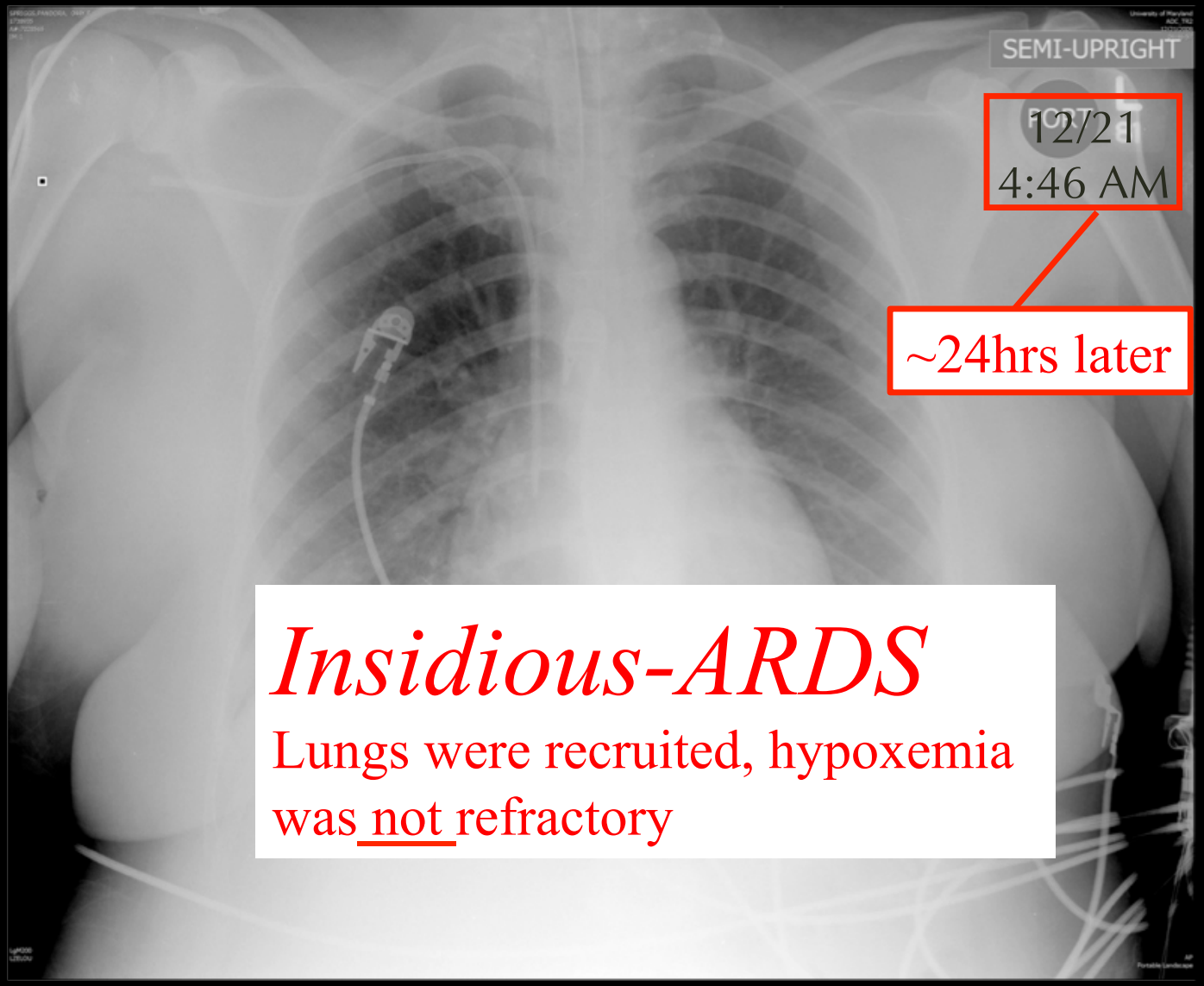
Insidious-ARDS

UPSTATE
MEDICAL UNIVERSITY



P/F ratio
<200

UPSTATE
MEDICAL UNIVERSITY



P/F ratio
>400

Insidious-ARDS

Lungs were recruited, hypoxemia was not refractory

UPSTATE
MEDICAL UNIVERSITY

Insidious-ARDS

- Unlike pregnancy ARDS is not binary but rather a disease with a progressive, insidious onset, similar to cancer

- *Insidious-ARDS* presents with identical symptoms as does *Established-ARDS*

- However, if the proper Mechanical Breath is applied to the lung with *Insidious-ARDS* the lung will reopen, edema will be reduced and oxygenation will return and disease progression may be halted

UPSTATE
MEDICAL UNIVERSITY

To Prevent ARDS we must Understand the Pathogenesis

- What is the role of mechanical ventilation in the development of *Established-ARDS*?
- Is there a 'treatment window' in the hospital during which ARDS can be treated?
- What is the progressive pulmonary pathophysiology as *EALI* evolves into *Established-ARDS* ?
  - *EALI* and *Insidious-ARDS* are progressive stages leading to *Established-ARDS*.
- What kind of mechanical breath is necessary to prevent ARDS?

UPSTATE
MEDICAL UNIVERSITY

To Prevent ARDS we must Understand the Pathogenesis

- What is the role of mechanical ventilation in the development of *Established-ARDS*?
- Is there a 'treatment window' in the hospital during which ARDS can be treated?
- What is the progressive pulmonary pathophysiology as *EALI* evolves into *Established-ARDS* ?
  - *EALI* and *Insidious-ARDS* are progressive stages leading to *Established-ARDS*.
- What kind of mechanical breath is necessary to prevent ARDS?

UPSTATE
MEDICAL UNIVERSITY

Before we can determine the components of the mechanical breath that may prevent the pathogenesis of ARDS we must know:

- The key pathologic components that drive progressive acute lung injury into ARDS

- Is the disease process propagated by a mechanical or inflammatory injury or both?

UPSTATE
MEDICAL UNIVERSITY

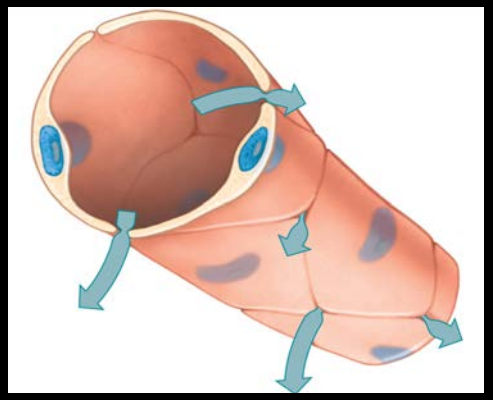
Before we can determine the components of the mechanical breath that may prevent the pathogenesis of ARDS we must know:

- The key pathologic components that drive progressive acute lung injury into ARDS

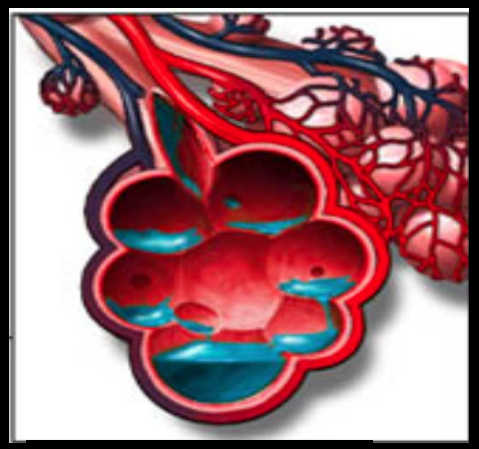
- Is the disease process propagated by a mechanical or inflammatory injury or both?

UPSTATE MEDICAL UNIVERSITY

Pathologic Tetrad of ARDS

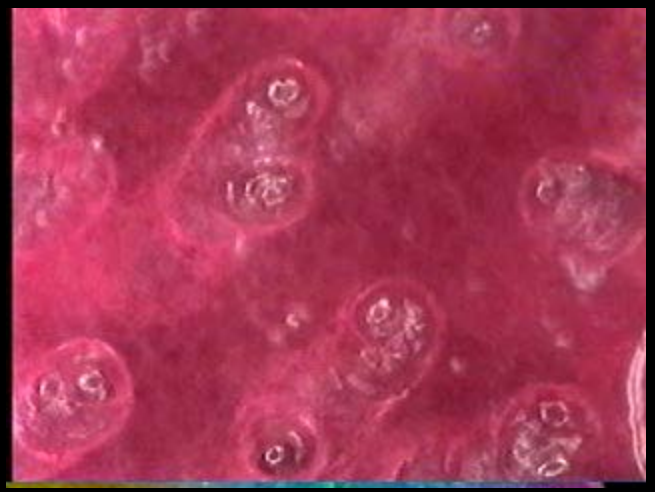


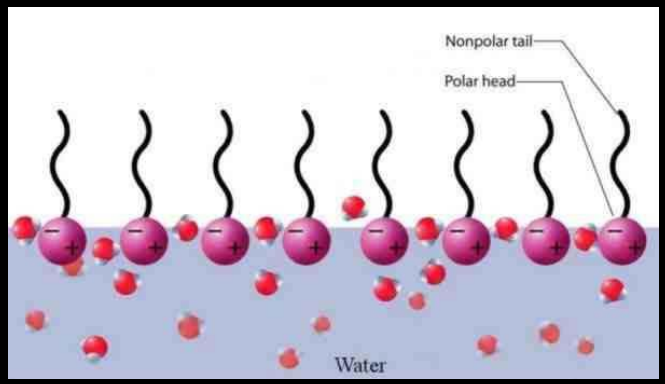
Appropriate P/T_P



Increased Capillary Permeability

Alveolar Edema





Alveolar Instability

Surfactant Deactivation

UPSTATE
MEDICAL UNIVERSITY

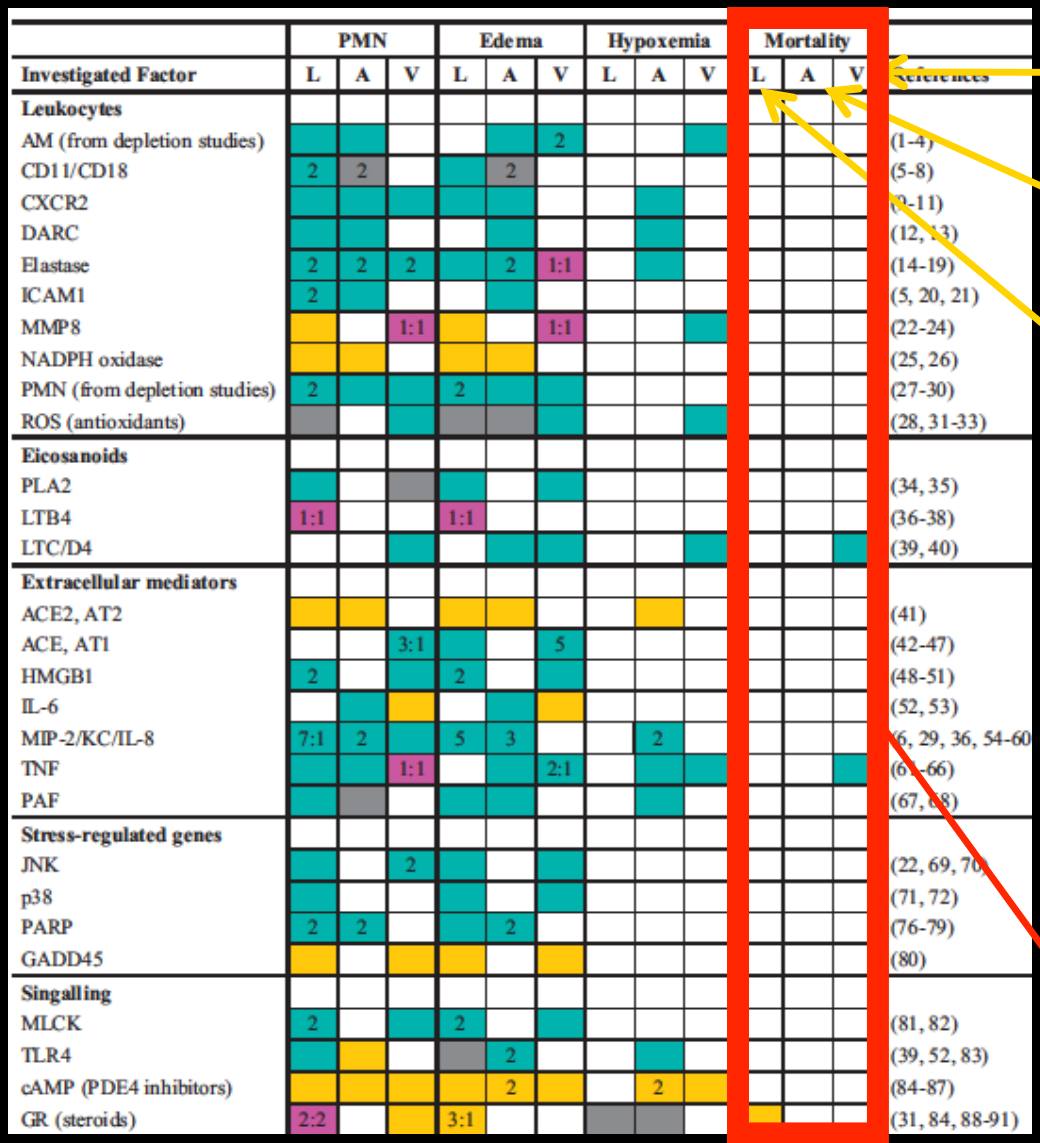
Before we can determine the components of the mechanical breath that may prevent the pathogenesis of ARDS we must know:

- The key pathologic components that drive progressive acute lung injury into ARDS

- Is the disease process propagated by a mechanical or inflammatory injury or both?

UPSTATE MEDICAL UNIVERSITY

ALI Models and Inflammatory Mediators



	PMN			Edema			Hypoxemia			Mortality			
Investigated Factor	L	A	V	L	A	V	L	A	V	L	A	V	References
Leukocytes													
AM (from depletion studies)						2							(1-4)
CD11/CD18	2	2			2								(5-8)
CXCR2													(9-11)
DARC													(12, 13)
Elastase	2	2	2		2	1:1							(14-19)
ICAM1	2												(5, 20, 21)
MMP8			1:1			1:1							(22-24)
NADPH oxidase													(25, 26)
PMN (from depletion studies)	2			2									(27-30)
ROS (antioxidants)													(28, 31-33)
Eicosanoids													
PLA2													(34, 35)
LTB4	1:1			1:1									(36-38)
LTC/D4													(39, 40)
Extracellular mediators													
ACE2, AT2													(41)
ACE, AT1			3:1			5							(42-47)
HMGB1	2			2									(48-51)
IL-6													(52, 53)
MIP-2/KC/IL-8	7:1	2		5	3			2					(6, 29, 36, 54-60)
TNF			1:1			2:1							(61-66)
PAF													(67, 68)
Stress-regulated genes													
JNK			2										(22, 69, 70)
p38													(71, 72)
PARP	2	2			2								(76-79)
GADD45													(80)
Singalling													
MLCK	2			2									(81, 82)
TLR4					2								(39, 52, 83)
cAMP (PDE4 inhibitors)					2			2					(84-87)
GR (steroids)	2:2			3:1									(31, 84, 88-91)

VILI

Acid Aspiration

Endotoxin - LPS

Grey = No effect

Yellow = Protective

Green = Contributing

Magenta = Contradictory

No Mortality Correlate!

Uhlig S. *European J Cell Bio* 2012

UPSTATE
MEDICAL UNIVERSITY

Mechanical Injury During Ventilation

Stress/Strain

UPSTATE
MEDICAL UNIVERSITY

Lung Stress and Strain During Mechanical Ventilation: Any Difference Between Statics and Dynamics?

Alessandro Protti, MD[1]; Davide T. Andreis, MD[1]; Massimo Monti, MD[1]; Alessandro Santini, MD[1]; Cristina C. Sparacino, MD[1]; Thomas Langer, MD[1]; Emiliano Votta, PhD[2]; Stefano Gatti, MD[3]; Luciano Lombardi, RT[4]; Orazio Leopardi, MD[1]; Serge Masson, PhD[5]; Massimo Cressoni, MD[1]; Luciano Gattinoni, MD FRCP[1,6].

Critical Care Medicine

January 2013 • Volume 41 • Number 2

UPSTATE
MEDICAL UNIVERSITY

What is Stress/Stain Injury, Really?

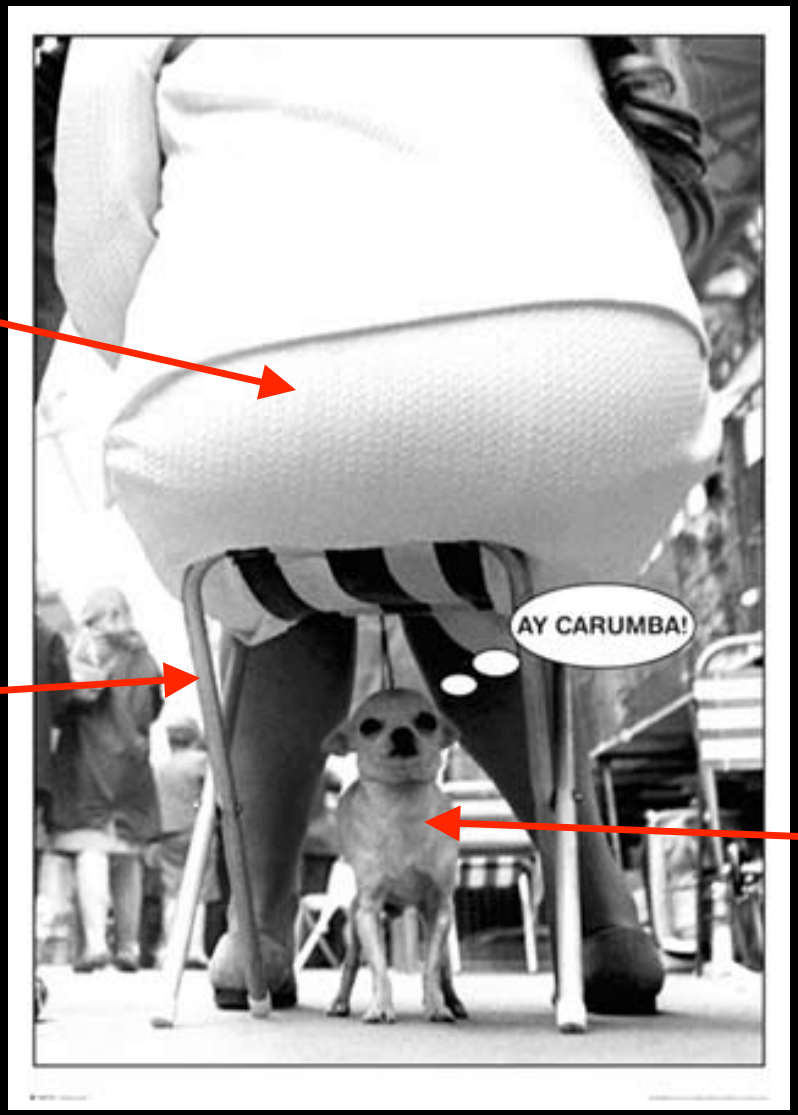
- Mechanical Stress
  - High airway pressure/shear stress (Volu- Atelectrauma)
- Exceeding the limits of the support structure
  - Alveolar and bronchiole walls
- Causing serious damage
  - VILI

UPSTATE
MEDICAL UNIVERSITY

Mechanism of VILI

Mechanical Stress

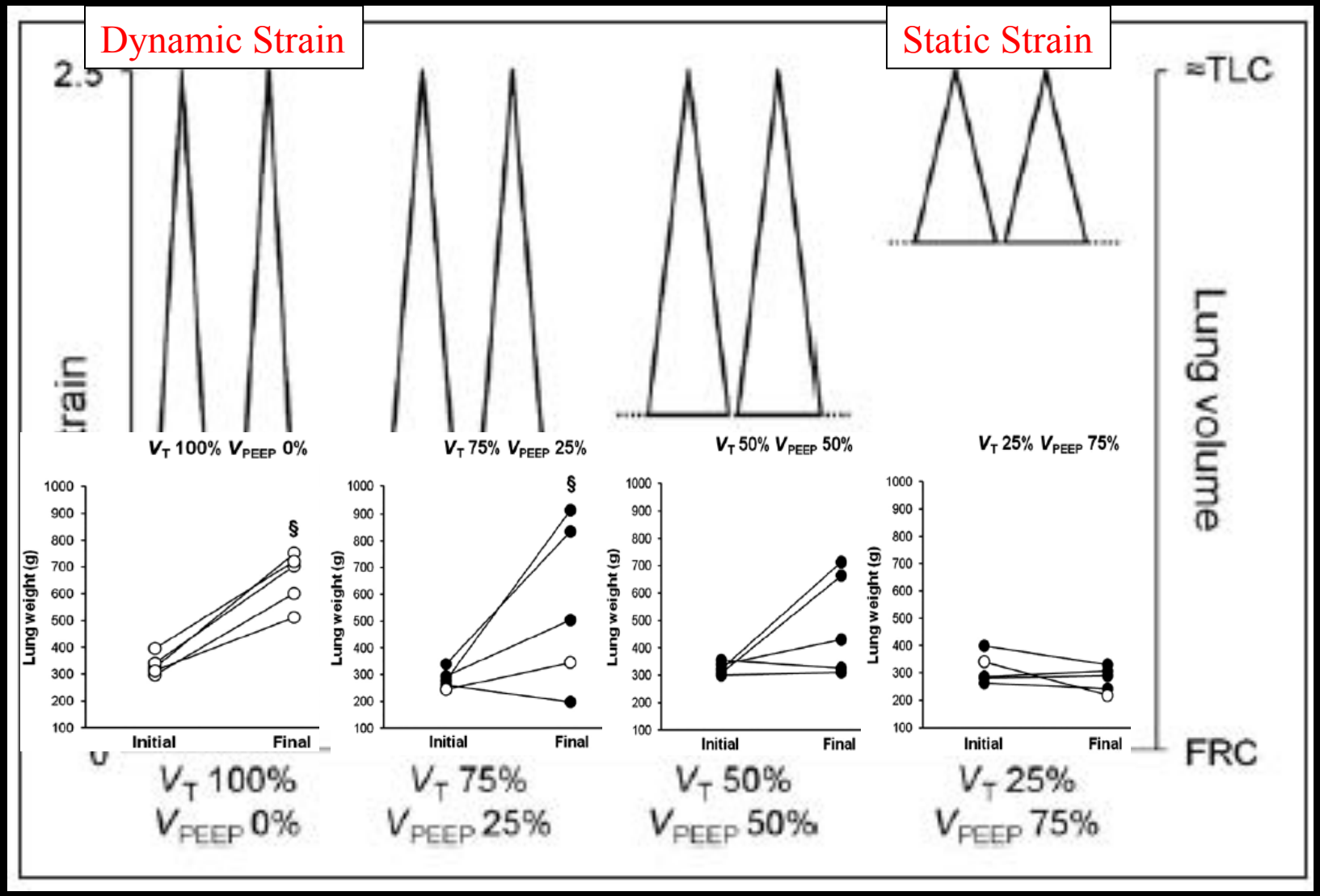
Support Structure



Serious Injury

UPSTATE MEDICAL UNIVERSITY

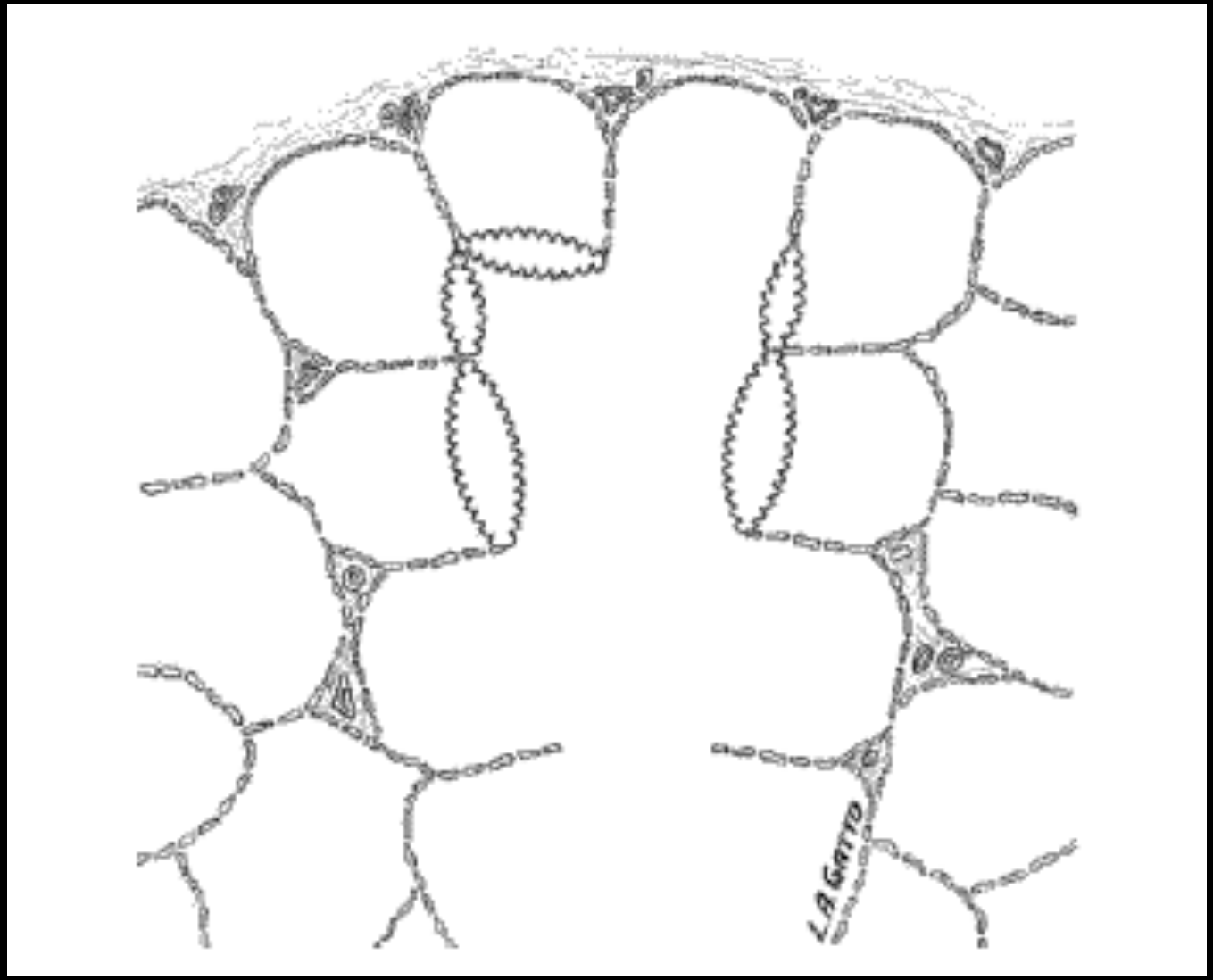
Study Protocol



Protti et al *Crit Care Med* 2013

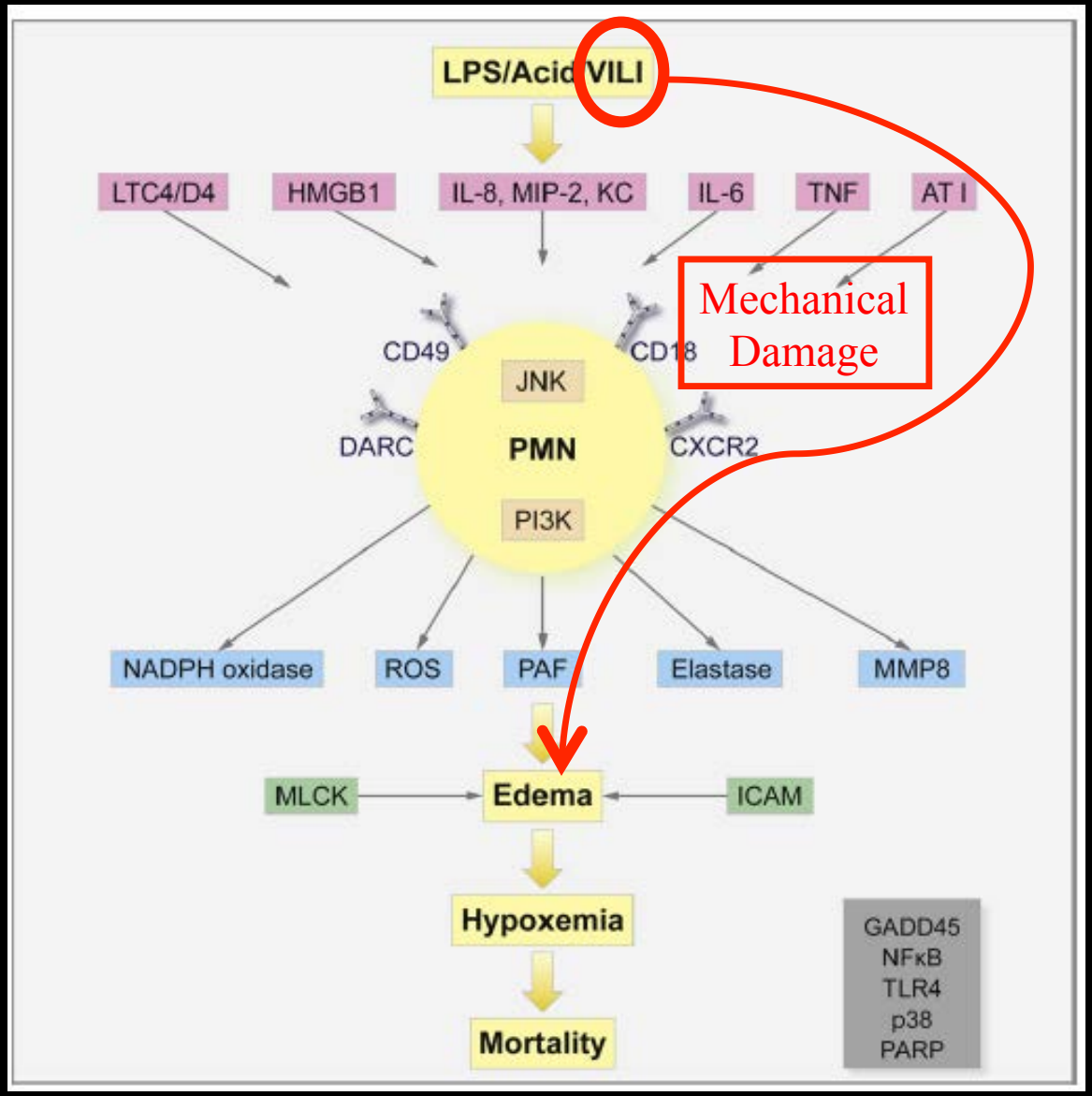
UPSTATE
MEDICAL UNIVERSITY

Shear Stress-Induced Alveolar Injury



UPSTATE
MEDICAL UNIVERSITY

Direct Injury by VILI



Uhlig S. *European J Cell Bio* 2012

UPSTATE
MEDICAL UNIVERSITY

Summary

- The 4 key pathologic components in ARDS pathogenesis are:
  - Increased capillary permeability
  - Surfactant deactivation
  - Alveolar edema
  - Alveolar instability (alveolar R/D)

- Mechanical damage caused by non-protective mechanical ventilation drives the progression of acute lung injury

UPSTATE
MEDICAL UNIVERSITY

Question

If mechanical ventilation is a primary driving force in progressive acute lung injury, how in the world can we use mechanical ventilation to prevent acute lung injury?

UPSTATE
MEDICAL UNIVERSITY

Take an Entirely New Approach

- Deconstruct the mechanical breath
  - Analyze all 10 components of the mechanical breath (pressures, flows, rates, volumes, *Times*)
  - Mechanical Breath Profile (MB_P)

- Determine the impact of any given MB_P on the Micro-environment – the alveoli and alveolar ducts

UPSTATE
MEDICAL UNIVERSITY

Take an Entirely New Approach

- Deconstruct the mechanical breath
  - Analyze all 10 components of the mechanical breath (pressures, flows, rates, volumes, *Times*)
  - Mechanical Breath Profile (MB_P)

- Determine the impact of any given MB_P on the Micro-environment – the alveoli and alveolar ducts

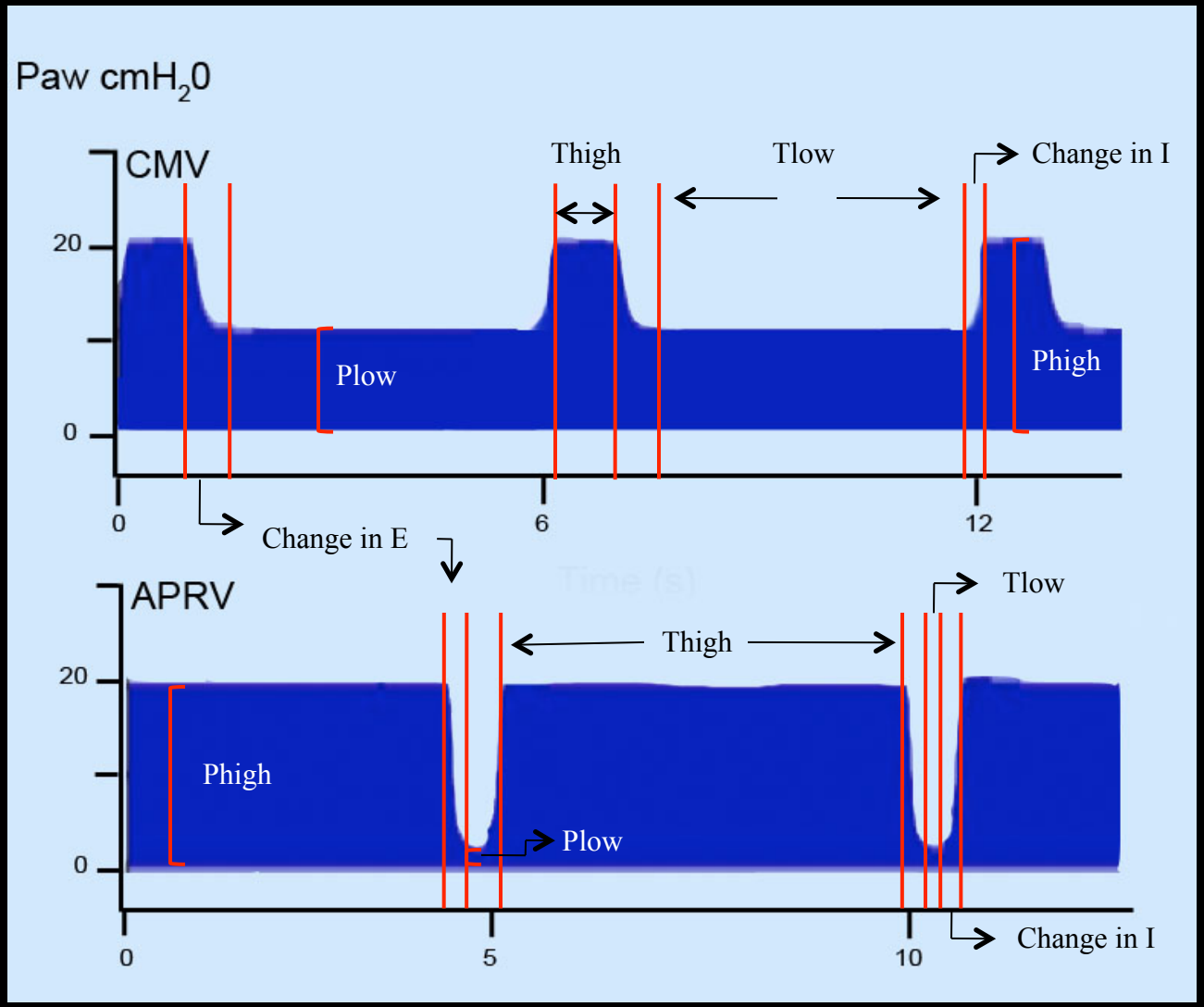
UPSTATE
MEDICAL UNIVERSITY

Whole Breath Deconstruction

- Time at Inspiration (T_I)
- Pressure at Inspiration (P_I)
- Time at Expiration (T_E)
- Pressure at Expiration (P_E)
- Transition Time from P_E to P_I (Inspiration rate - ΔP_I)
- Transition Time from P_I to P_E (Expiration rate - ΔP_E)
- Respiratory Rate
- Tidal Volume
- Inspiratory Flow
- Expiratory Flow
- FRC
- TLC

UPSTATE MEDICAL UNIVERSITY

Whole Breath Deconstruction



UPSTATE
MEDICAL UNIVERSITY

First Step in Whole Breath Analysis

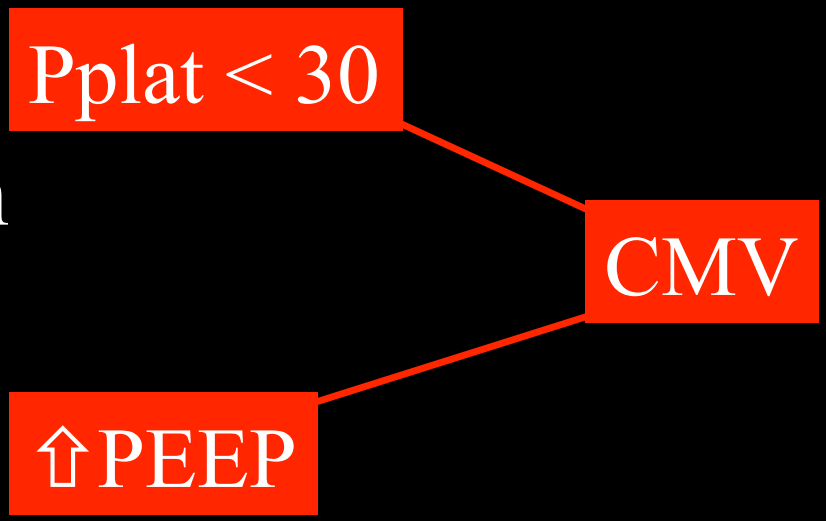
Identify the role of *Time* on lung protection

Pressure/Time Profile: P/T_P

UPSTATE
MEDICAL UNIVERSITY

Components Comprising the P/T_P

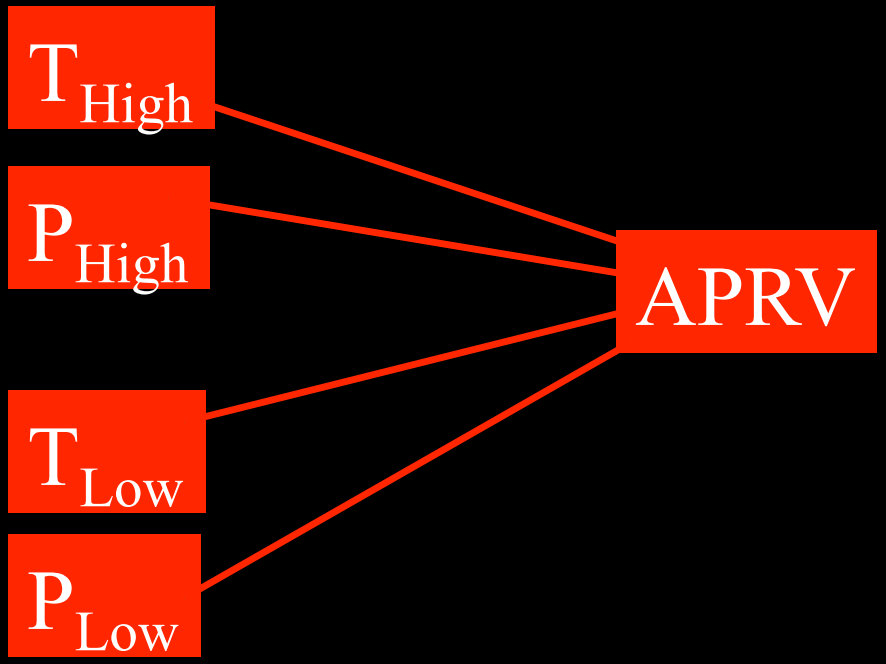
- Inspiration
  - Time
  - Pressure
- Expiration
  - Time
  - Pressure
- RATE of change between Inspiration and Expiration



UPSTATE
MEDICAL UNIVERSITY

Components Comprising the P/T_P

- Inspiration
  - Time
  - Pressure
- Expiration
  - Time
  - Pressure
- RATE of change between Inspiration and Expiration



UPSTATE
MEDICAL UNIVERSITY

We used the APRV mode in our experiments due to the ease of setting the *Time* of pressure application throughout the mechanical breath

UPSTATE
MEDICAL UNIVERSITY

Ventilator as a Therapeutic Tool to Prevent ARDS

- Maintain a fully inflated homogeneously ventilated lung
  - APRV extended *time* at inspiration (T_{High}) continually recruits
- Prevent alveolar collapse during expiration
  - APRV very short *time* a expiration (T_{Low}) prevents collapse

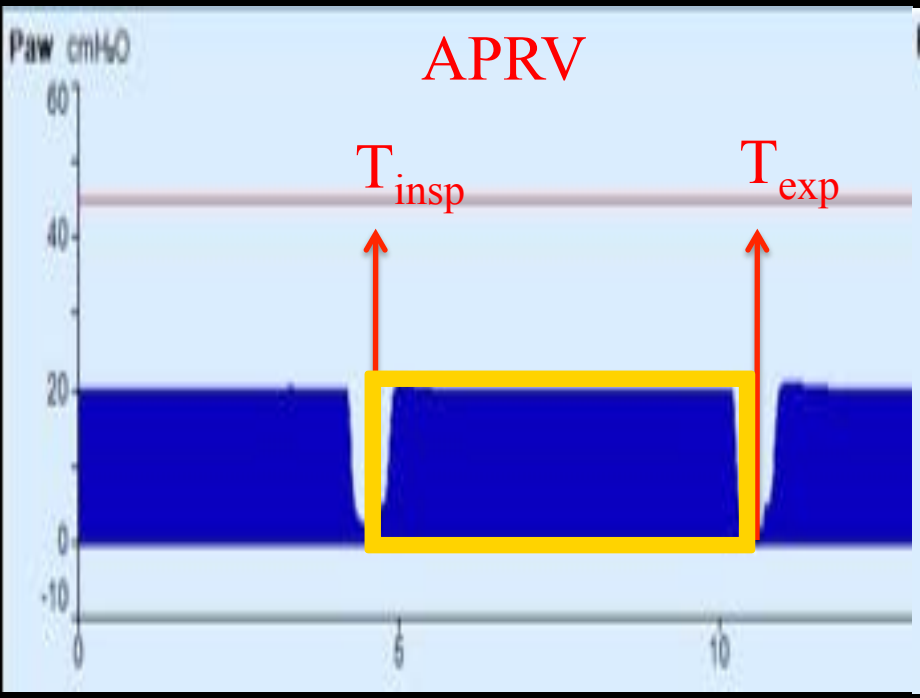
UPSTATE
MEDICAL UNIVERSITY

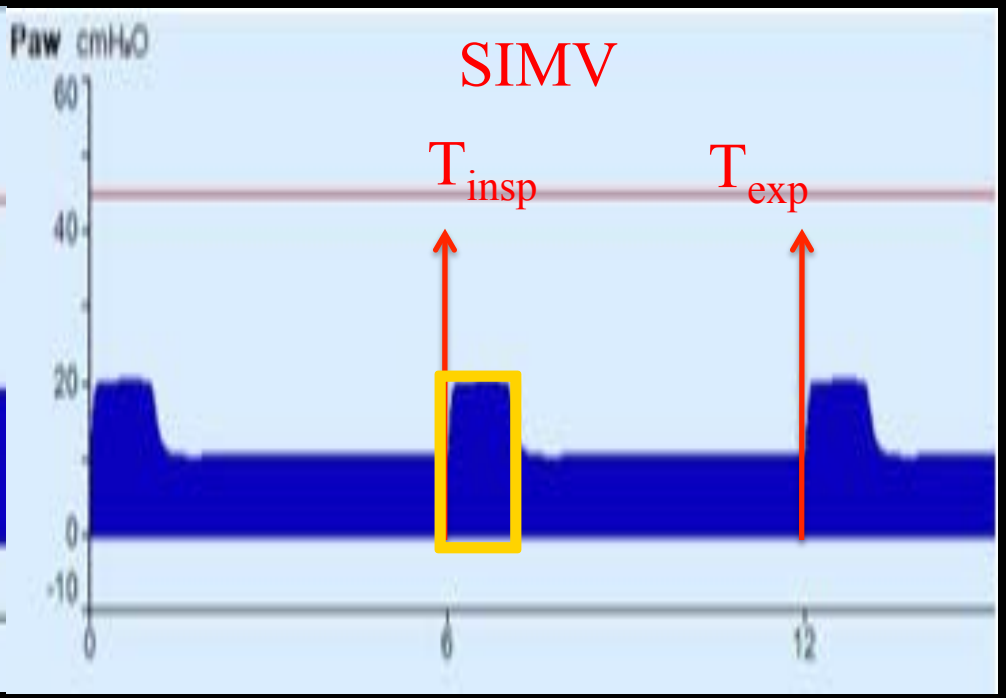
Ventilator as a Therapeutic Tool to Prevent ARDS

- Maintain a fully inflated homogeneously ventilated lung
  - APRV extended *time* at inspiration (T_{High}) continually recruits
- Prevent alveolar collapse during expiration
  - APRV very short *time* a expiration (T_{Low}) prevents collapse

UPSTATE
MEDICAL UNIVERSITY

The Pressure Time Profile (P/T_P) describes the airway pressure profile of the *Entire Breath* over the time period of one respiratory cycle. P/T_P is the area under the airway pressure curve.





$$P/T_P = \int_{T_{insp}}^{T_{exp}} P\,dT$$

Roy et al *J Trauma Acute Care Surg.* 2012,73: 391

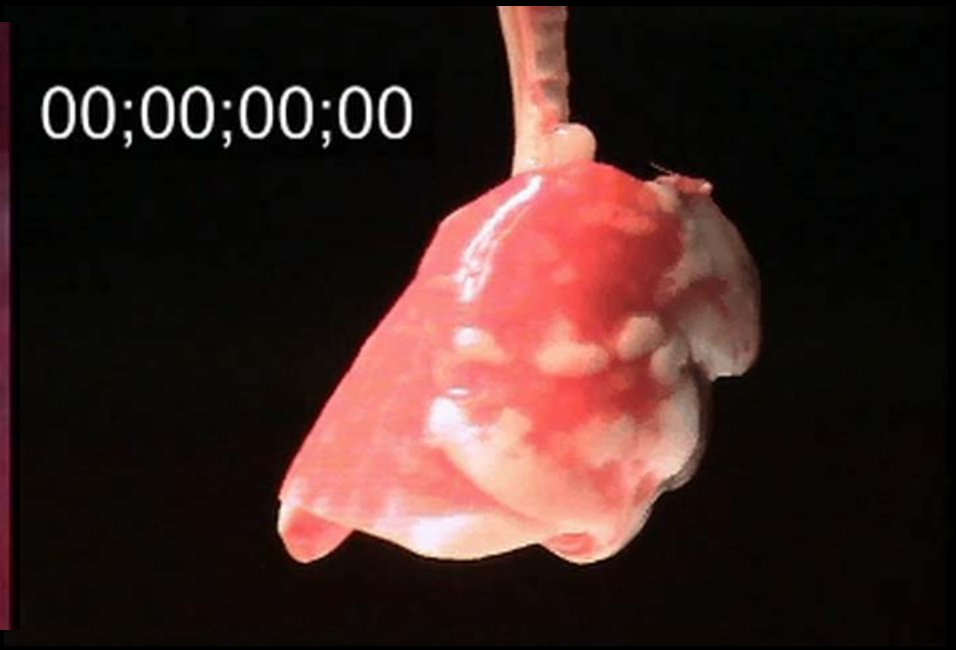
UPSTATE
MEDICAL UNIVERSITY

Two Basic Components of P/T_P

- Pressure
- Time

UPSTATE
MEDICAL UNIVERSITY

The Effects of Pressure and Time



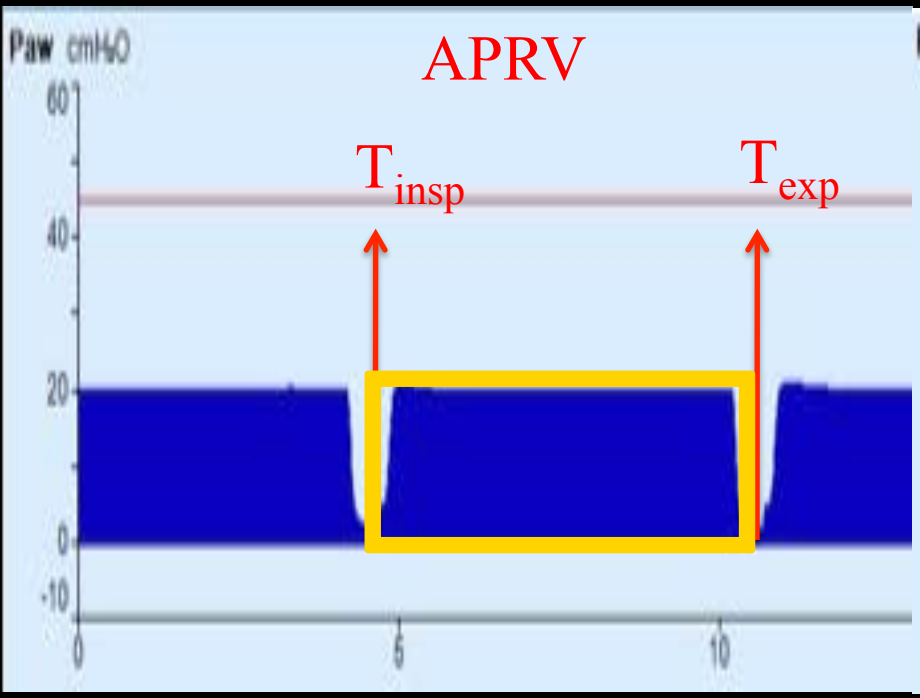
Pressure = 40 cm H_2O

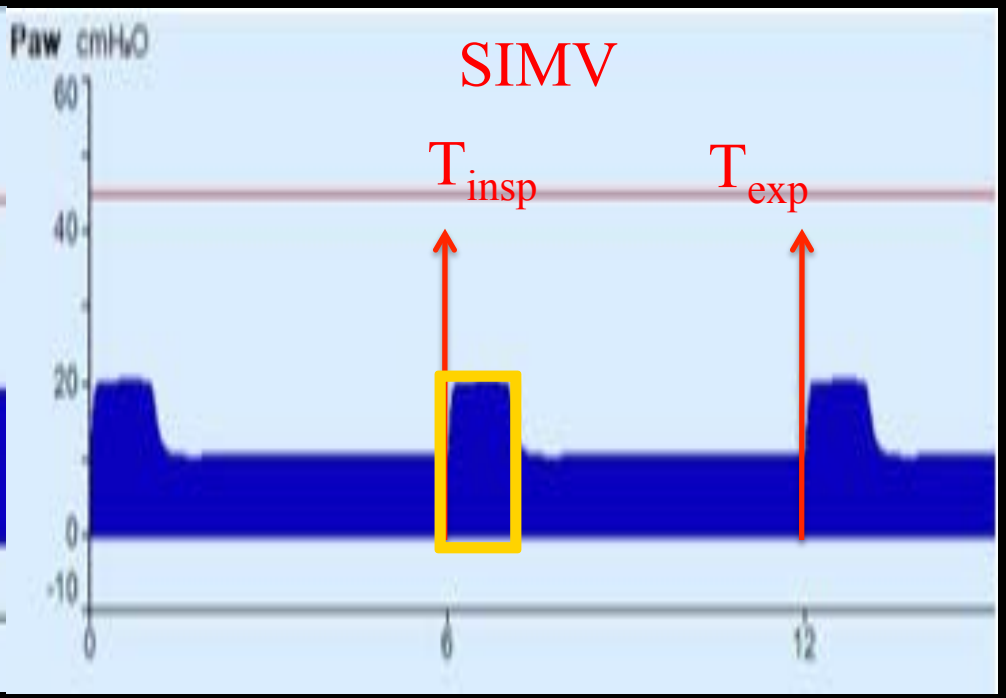
Time = 40 seconds

Albert SP et al *J Appl Physiol*, 2009

UPSTATE
MEDICAL UNIVERSITY

The Pressure Time Profile (P/T_P) describes the airway pressure profile of the *Entire Breath* over the time period of one respiratory cycle. P/T_P is the area under the airway pressure curve.





$$P/T_P = \int_{T_{insp}}^{T_{exp}} P\,dT$$

Roy et al *J Trauma Acute Care Surg.* 2012,73: 391

UPSTATE
MEDICAL UNIVERSITY

Ventilator as a Therapeutic Tool to Prevent ARDS

- Maintain a fully inflated homogeneously ventilated lung
  - APRV extended *time* at inspiration (T_{High}) continually recruits
- Prevent alveolar collapse during expiration
  - APRV very short *time* a expiration (T_{Low}) prevents collapse

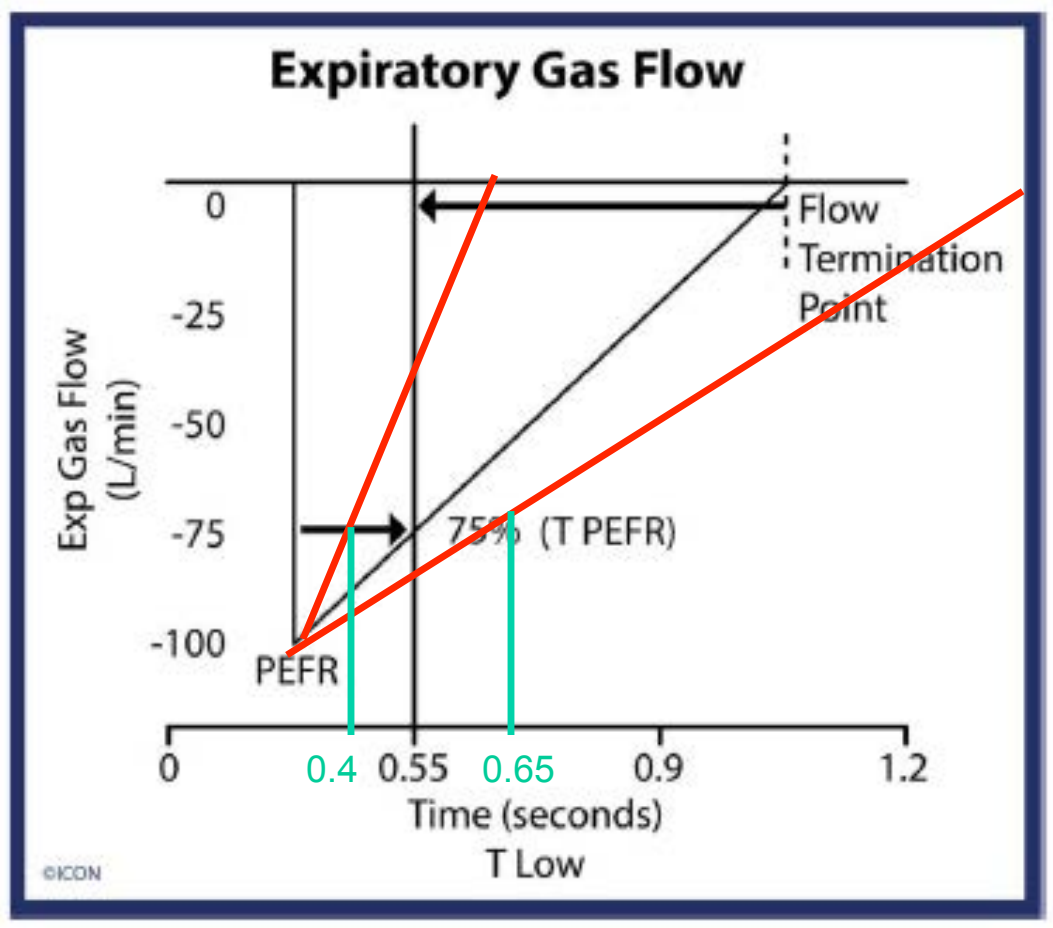
UPSTATE
MEDICAL UNIVERSITY

Ventilator as a Therapeutic Tool to Prevent ARDS

- Maintain a fully inflated homogeneously ventilated lung
  - APRV extended *time* at inspiration (T_{High}) continually recruits
- Prevent alveolar collapse during expiration
  - APRV very short *time* a expiration (T_{Low}) prevents collapse

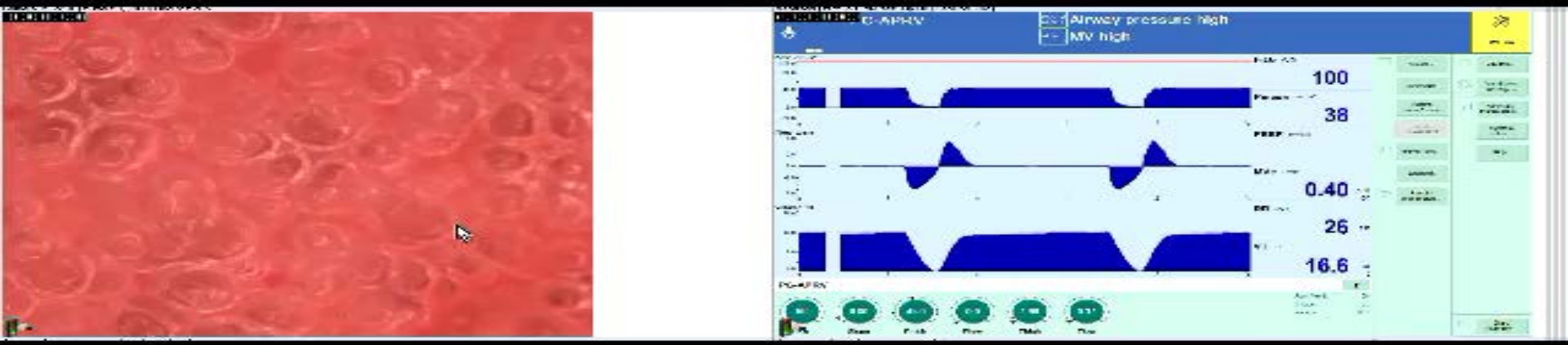
UPSTATE
MEDICAL UNIVERSITY

T_{Low} Set by a Physiologic Closed Loop Feedback System



UPSTATE
MEDICAL UNIVERSITY

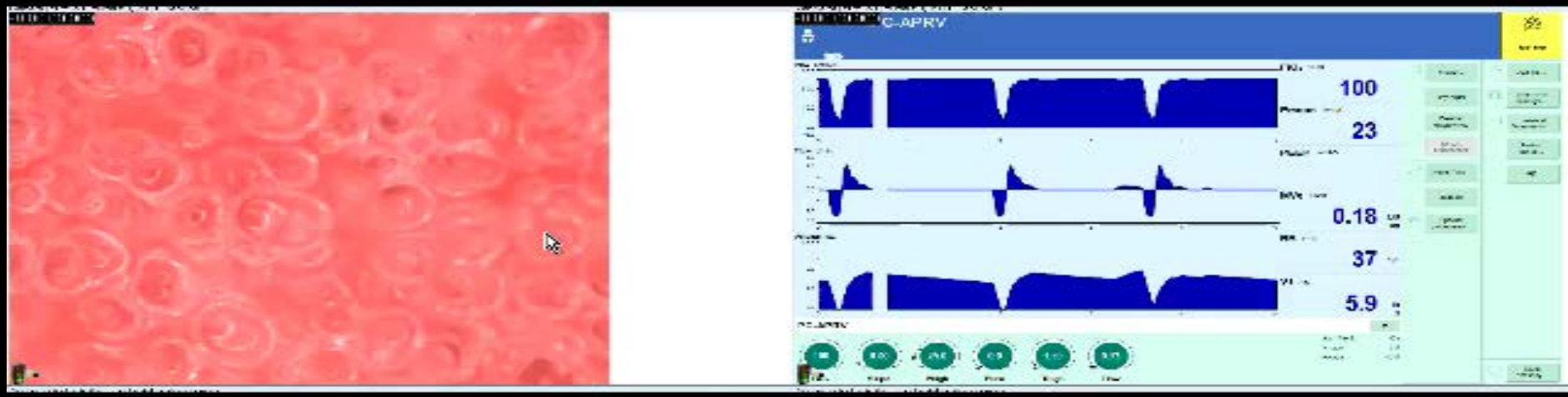
APRV



Tlow set incorrectly at 10% of Peak Expiratory Flow Rate

UPSTATE
MEDICAL UNIVERSITY

APRV



Tlow set correctly at 75% of Peak Expiratory Flow Rate

UPSTATE
MEDICAL UNIVERSITY

Ventilator as a Therapeutic Tool to Prevent ARDS

- Maintain a fully inflated homogeneously ventilated lung
  - APRV extended *time* at inspiration (T_{High}) continually recruits
- Prevent alveolar collapse during expiration
  - APRV very short *time* a expiration (T_{Low}) prevents collapse

UPSTATE
MEDICAL UNIVERSITY

Current Studies in our Lab

Mechanical Breath Profile (MB_P)

UPSTATE
MEDICAL UNIVERSITY

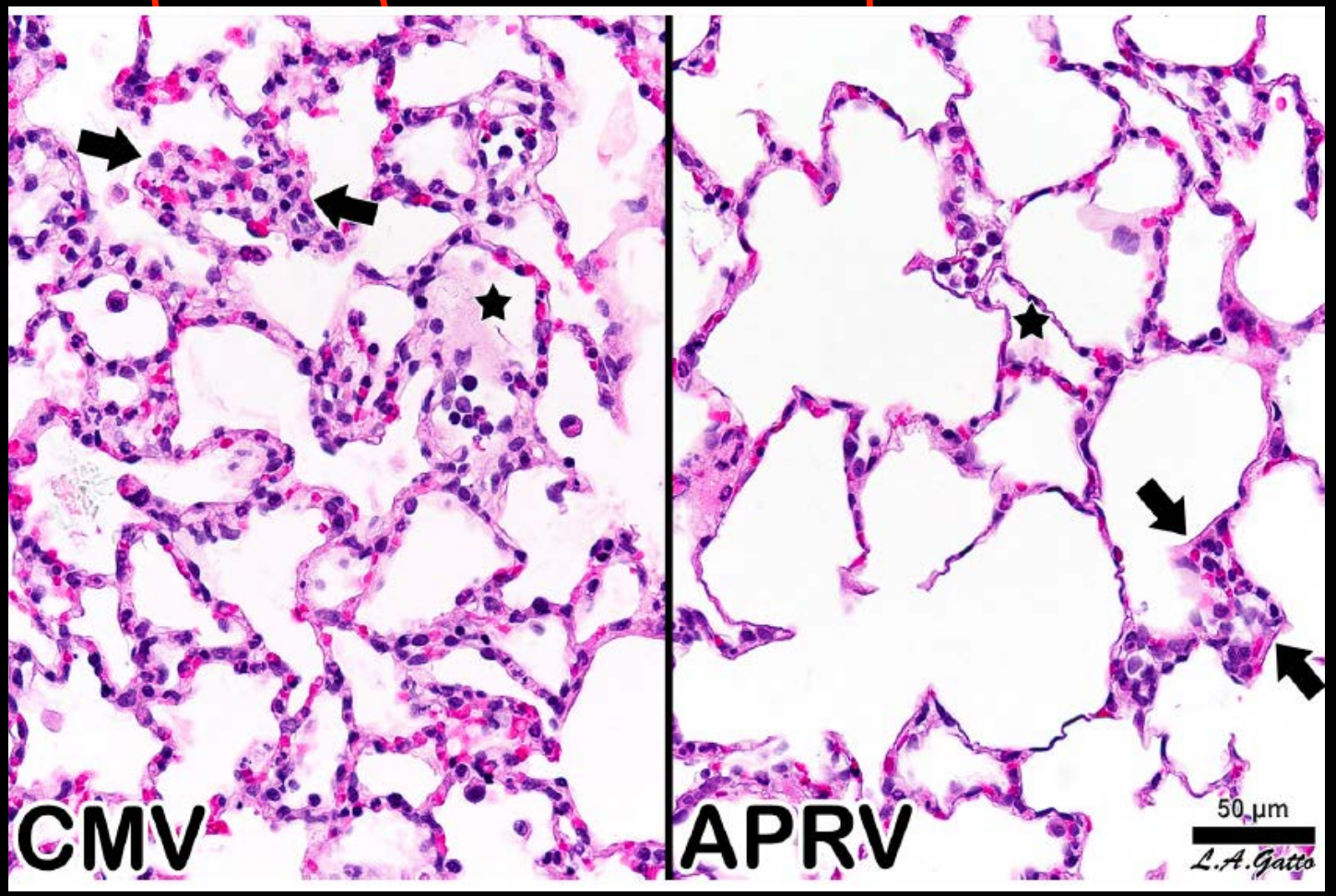
Whole Breath Analysis

- Time at Inspiration (T_I)
- Pressure at Inspiration (P_I)
- Time at Expiration (T_E)
- Pressure at Expiration (P_E)
- Transition Time from P_E to P_I (Inspiration rate - ΔP_I)
- Transition Time from P_I to P_E (Expiration rate - ΔP_E)
- Respiratory Rate
- Tidal Volume
- Inspiratory Flow
- Expiratory Flow
- FRC
- TLC

UPSTATE
MEDICAL UNIVERSITY

MBp	Time at Insp	Time at Exp	ΔT_E	Press at Insp	Tidal Vol	Q_E
Rho	0.8178	-0.8234	-0.8321	-0.8419	0.8	-0.8763
p value	0.0468	0.0440	0.0398	0.0355	0.0495	0.0220

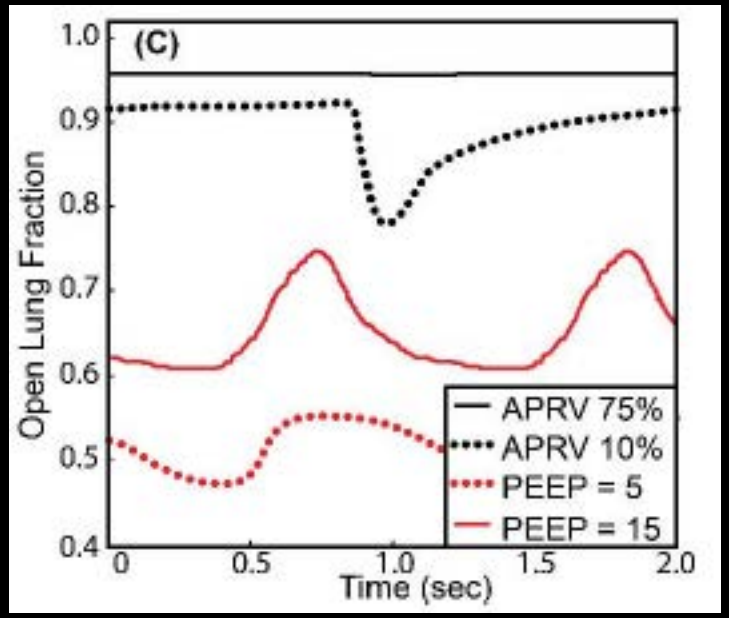
APRV



UPSTATE
MEDICAL UNIVERSITY

Smith B et al BMES, Abstract, 2014

Physiologically-based Computational Model



- Short time at low pressure with APRV-75% doses not allow time for derecruitment
- Long time at high pressure with APRV-75% improves lung recruitment
- Thus, APRV-75% opens the lung for homogeneous ventilation and prevents alveolar collapse and instability

UPSTATE
MEDICAL UNIVERSITY

Conclusion

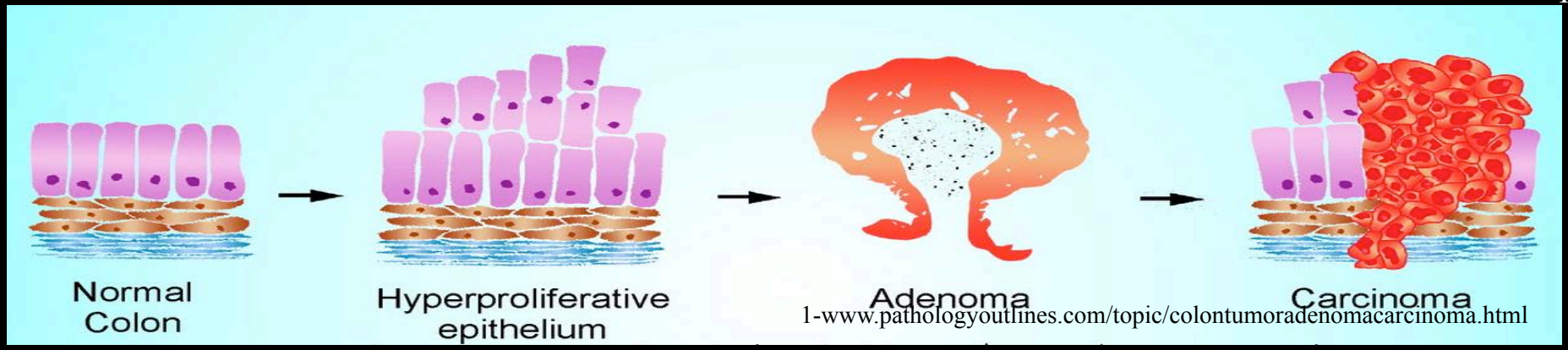
- Multiple components in the Mechanical breath including:
  - Time a peak inspiration (very long)
  - Time at end expiration (very short)
  - Pressure at inspiration (low)
  - Tidal volume (high)

UPSTATE
MEDICAL UNIVERSITY

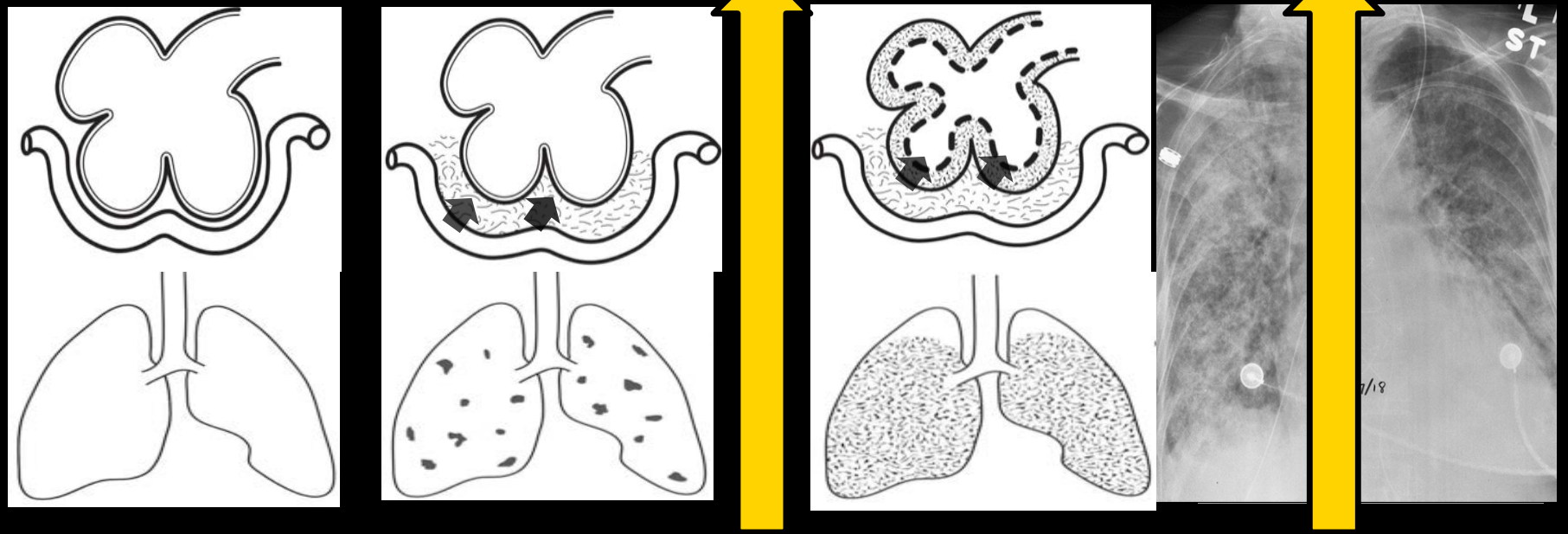
Preemptive ventilation to prevent ARDS: Studies from our Lab

UPSTATE
MEDICAL UNIVERSITY

Rationale for Prevention



1-www.pathologyoutlines.com/topic/colontumoradenomacarcinoma.html



Preemptive Intervention **Present Intervention**

UPSTATE
MEDICAL UNIVERSITY

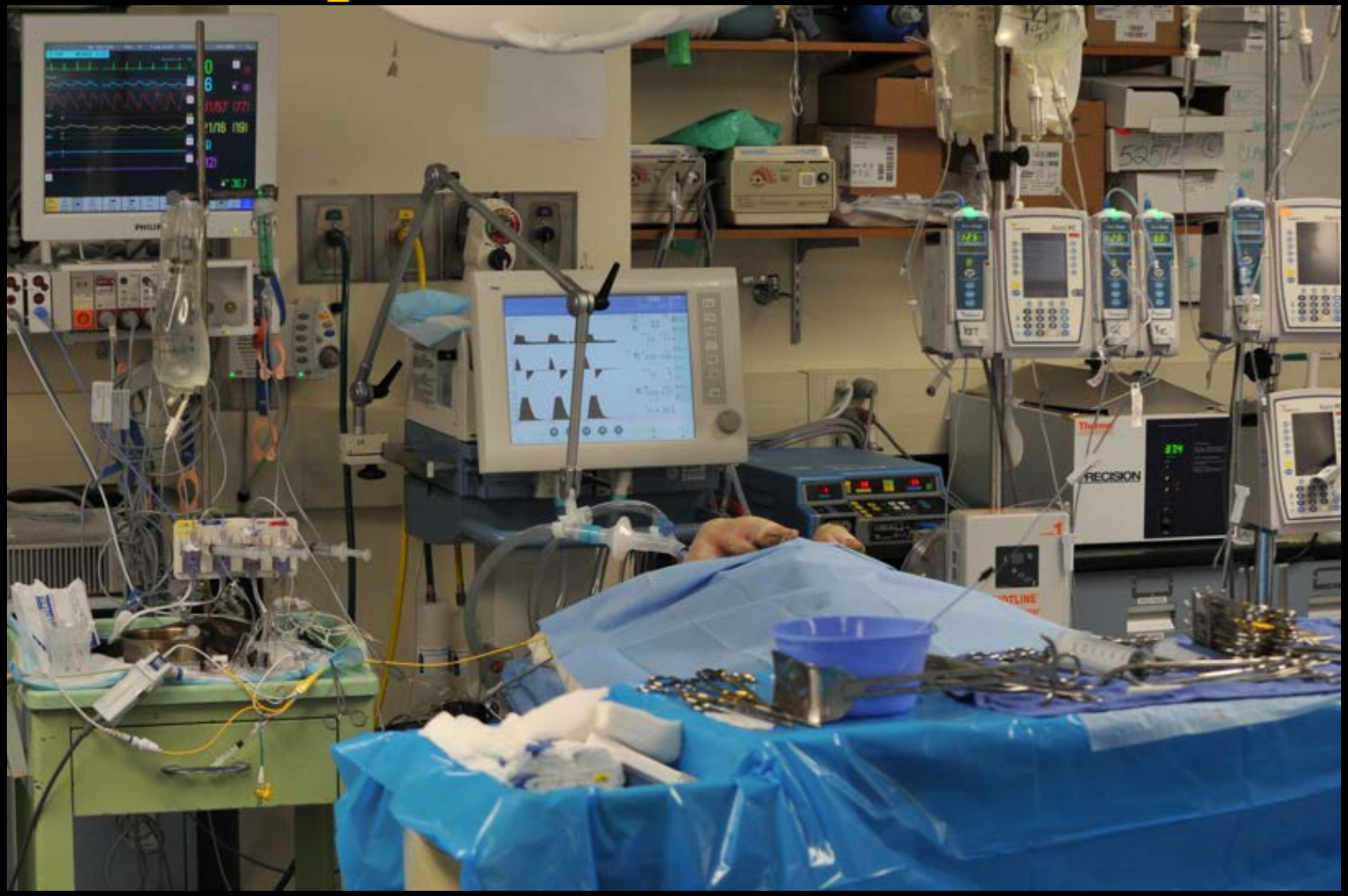
SHOCK, Vol. 39, No. 1, pp. 28–38, 2013

EARLY AIRWAY PRESSURE RELEASE VENTILATION PREVENTS ARDS—A NOVEL PREVENTIVE APPROACH TO LUNG INJURY

Shreyas Roy,* Nader Habashi,† Benjamin Sadowitz,* Penny Andrews,† Lin Ge,* Guirong Wang,* Preyas Roy,‡ Auyon Ghosh,* Michael Kuhn,§ Joshua Satalin,* Louis A. Gatto,‖ Xin Lin,¶ David A. Dean,¶ Yoram Vodovotz,** and Gary Nieman*

UPSTATE
MEDICAL UNIVERSITY

Our Model: '2-Hit' Peritoneal Sepsis +I/R Induced ARDS



UPSTATE
MEDICAL UNIVERSITY

Experimental Design:

Surgical Instrumentation

2-Hit Injury

APRV (n=4)

- $P_{high} = P_{plat}$
- $P_{low} = 0$
- T_{low} PEFR = 75%
- T_{high} = > 90% CPAP
- Vt = 12 mL/kg

Sham (n=5)

- PEEP = 5
- Vt = 10 mL/kg
- No Sepsis+I/R

ARDSnet (n=3)

- High PEEP Scale
- Vt = 6 mL/kg
- Applied post ↓ O_2

Broad Spectrum Antibiotics

Early Goal Directed Therapy Based Fluid Resuscitation and Vasopressors

All Animals Continuously Monitored according to ICU Standards of Care

Roy et al *Shock* 2013;39: 28

UPSTATE
MEDICAL UNIVERSITY

Results

- All Pigs Developed Septic Shock
  - Fever, Leukopenia
  - Hemodynamic Compromise
  - Positive Blood Cultures
    - *E Coli, Pseudomonas, Streptococci, Klebsiella pneumoniae*

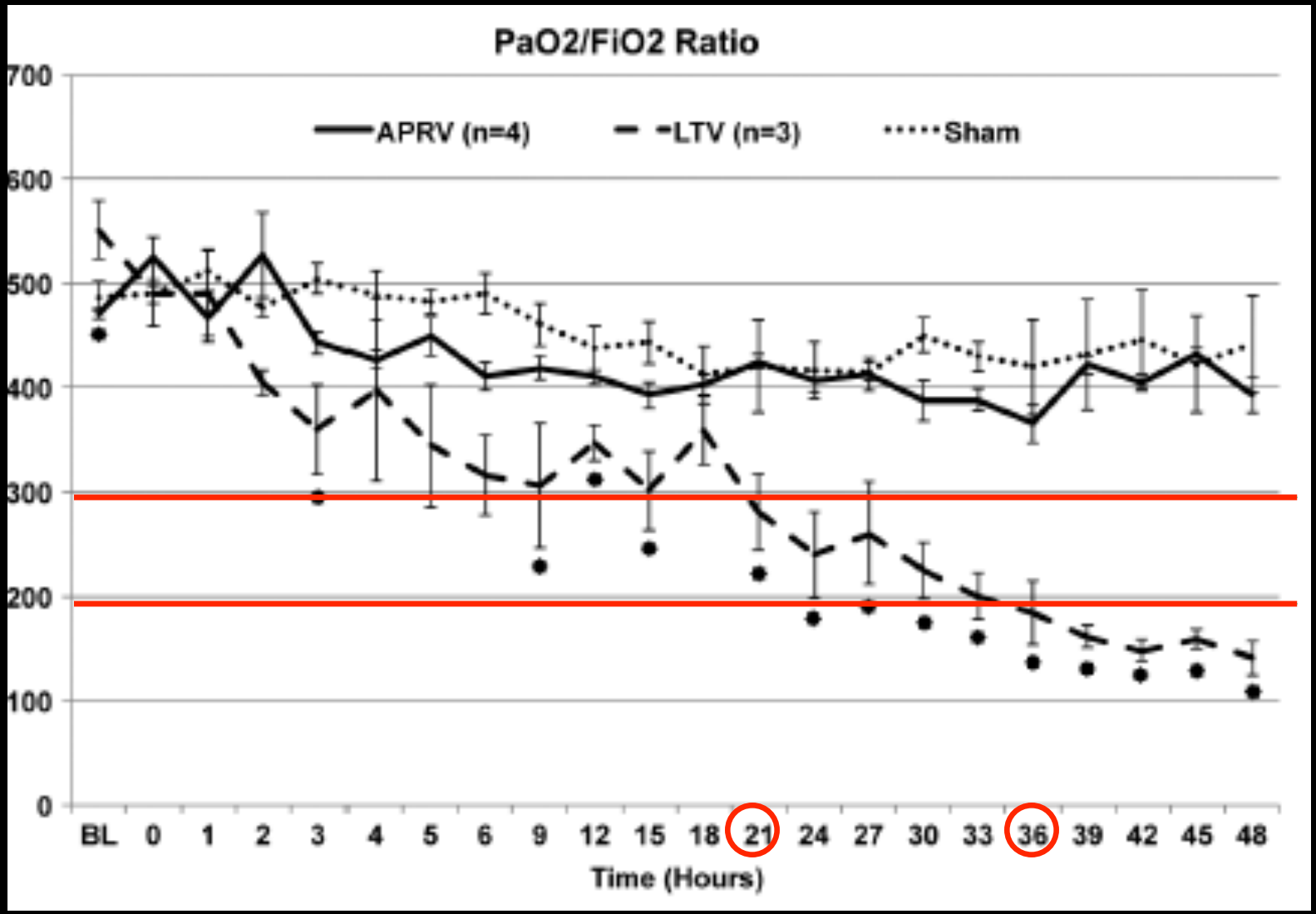
- All Pigs Developed Complications of Shock:
- Abdominal Compartment Syndrome
  - Gastric Stress Ulcers
  - Sepsis Associated Coagulopathy
  - Oliguric Renal Failure

SOFA scores & plasma IL-6 were not different

Roy et al *Shock* 2013;39: 28

UPSTATE
MEDICAL UNIVERSITY

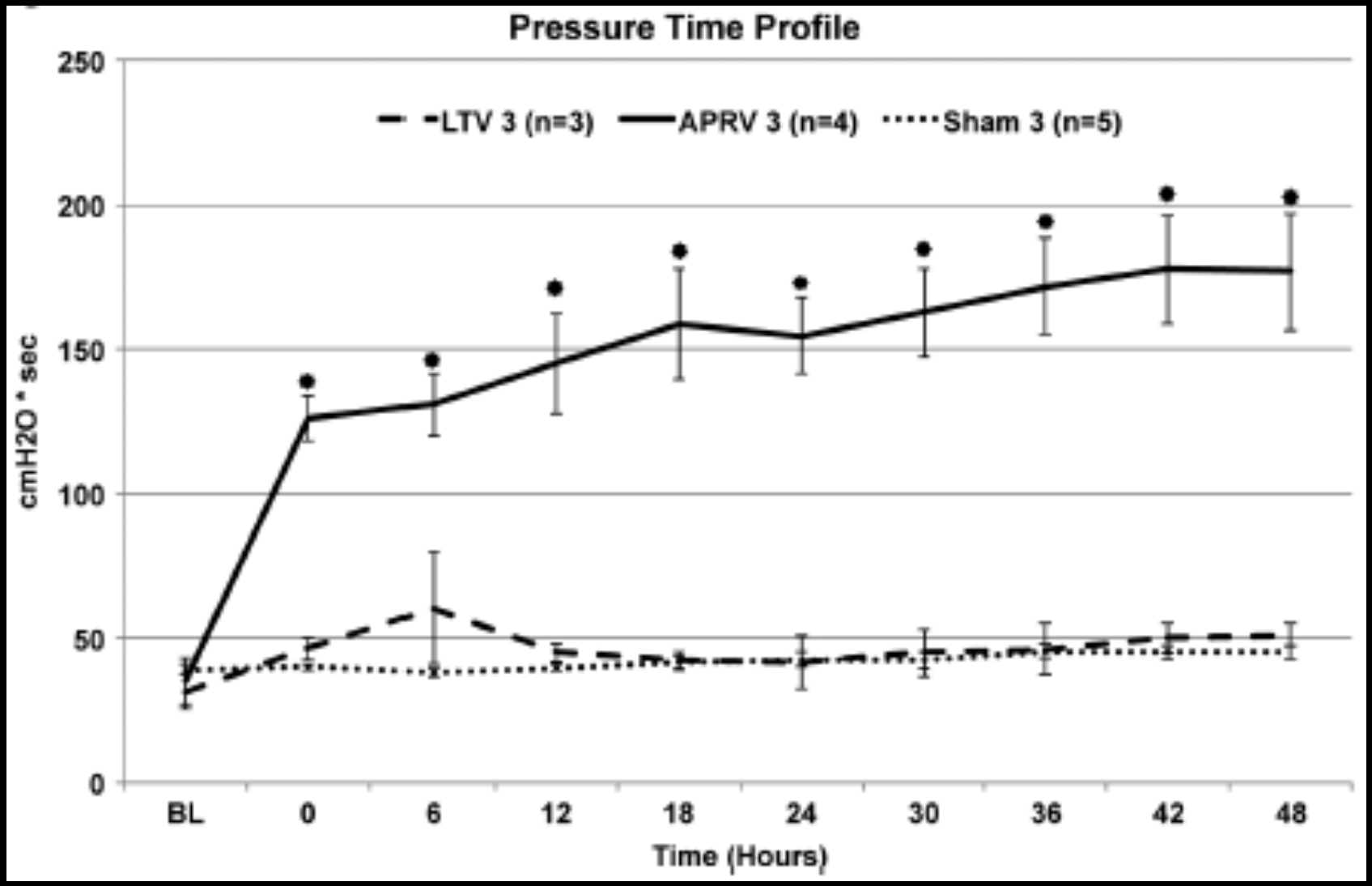
PaO_2/FiO_2 Ratio



Roy et al *Shock* 2013;39: 28

UPSTATE
MEDICAL UNIVERSITY

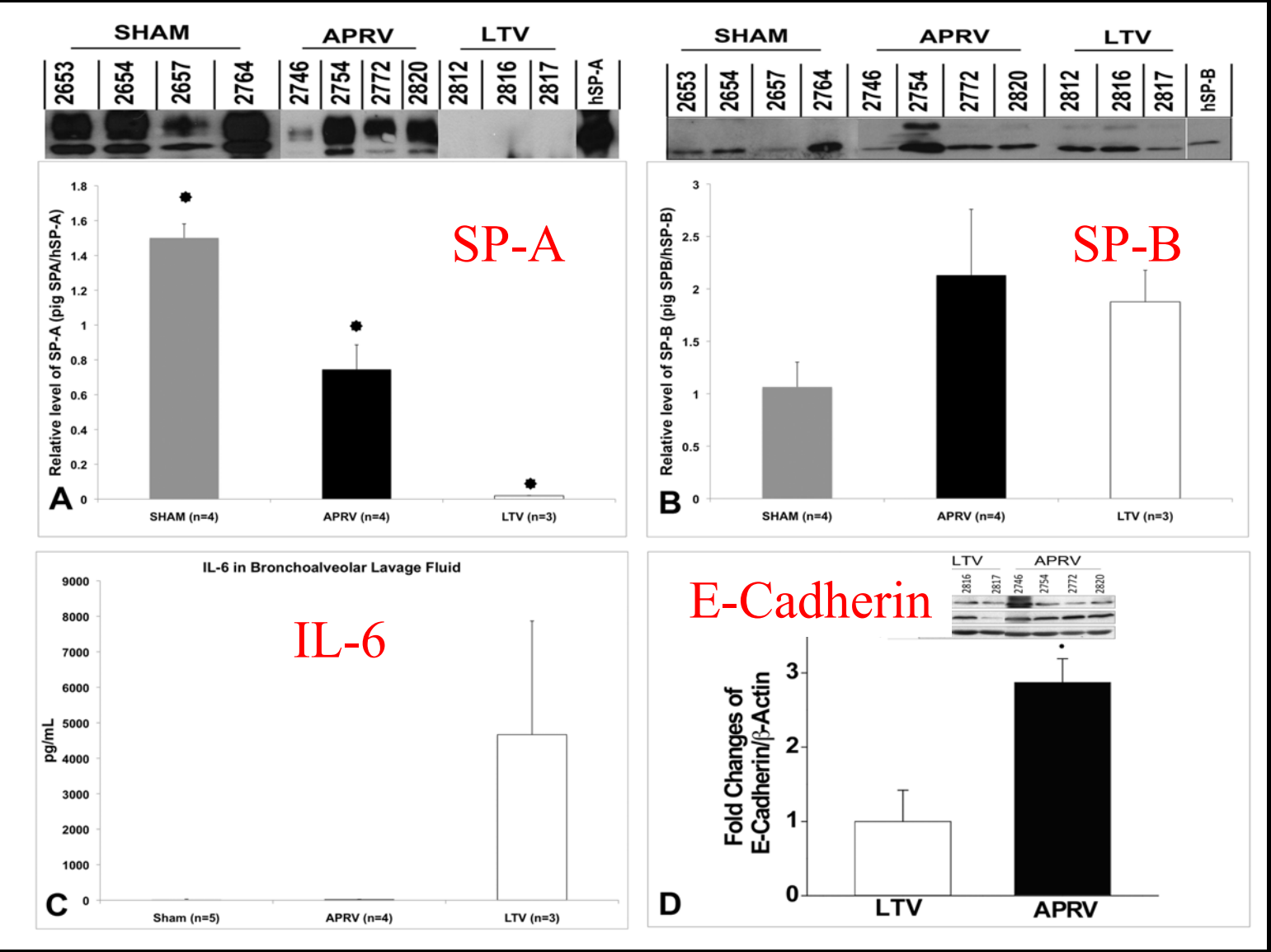
Pressure/Time Profile (P/T_p)



Roy et al *Shock* 2013;39: 28

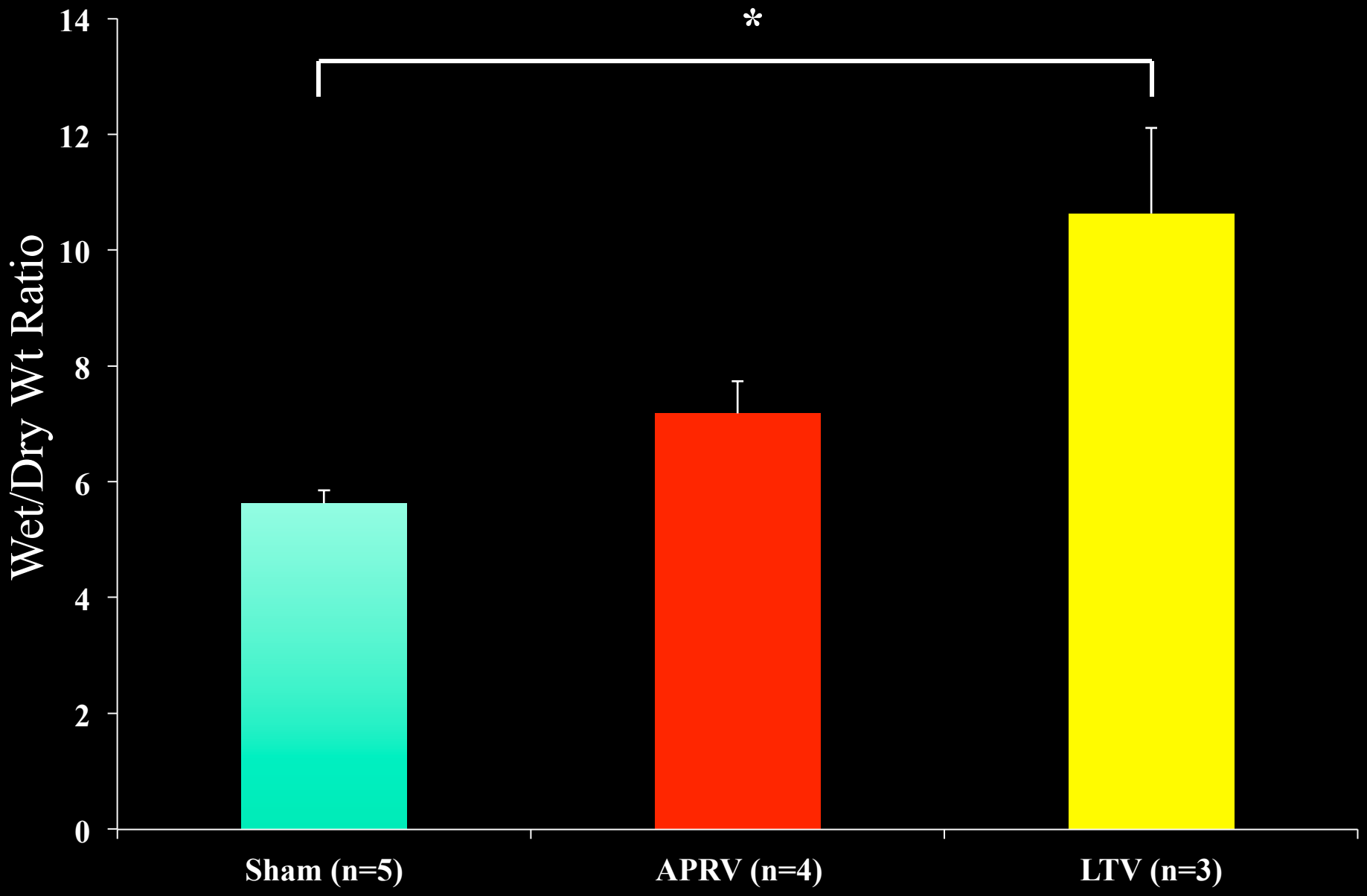
UPSTATE
MEDICAL UNIVERSITY

Molecular Protection



UPSTATE
MEDICAL UNIVERSITY

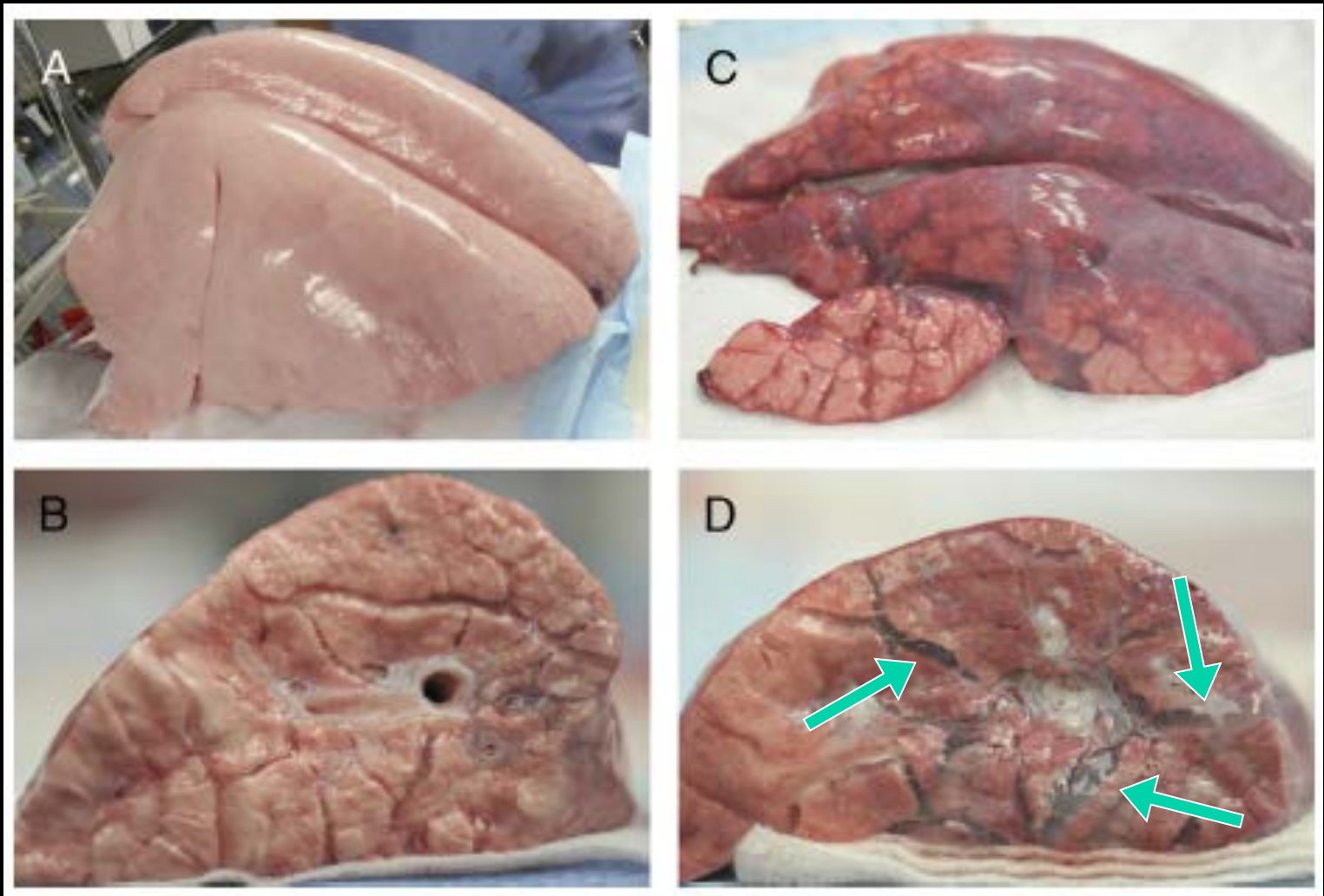
Pulmonary Edema



UPSTATE
MEDICAL UNIVERSITY

Gross Lung

APRV ARDSnet

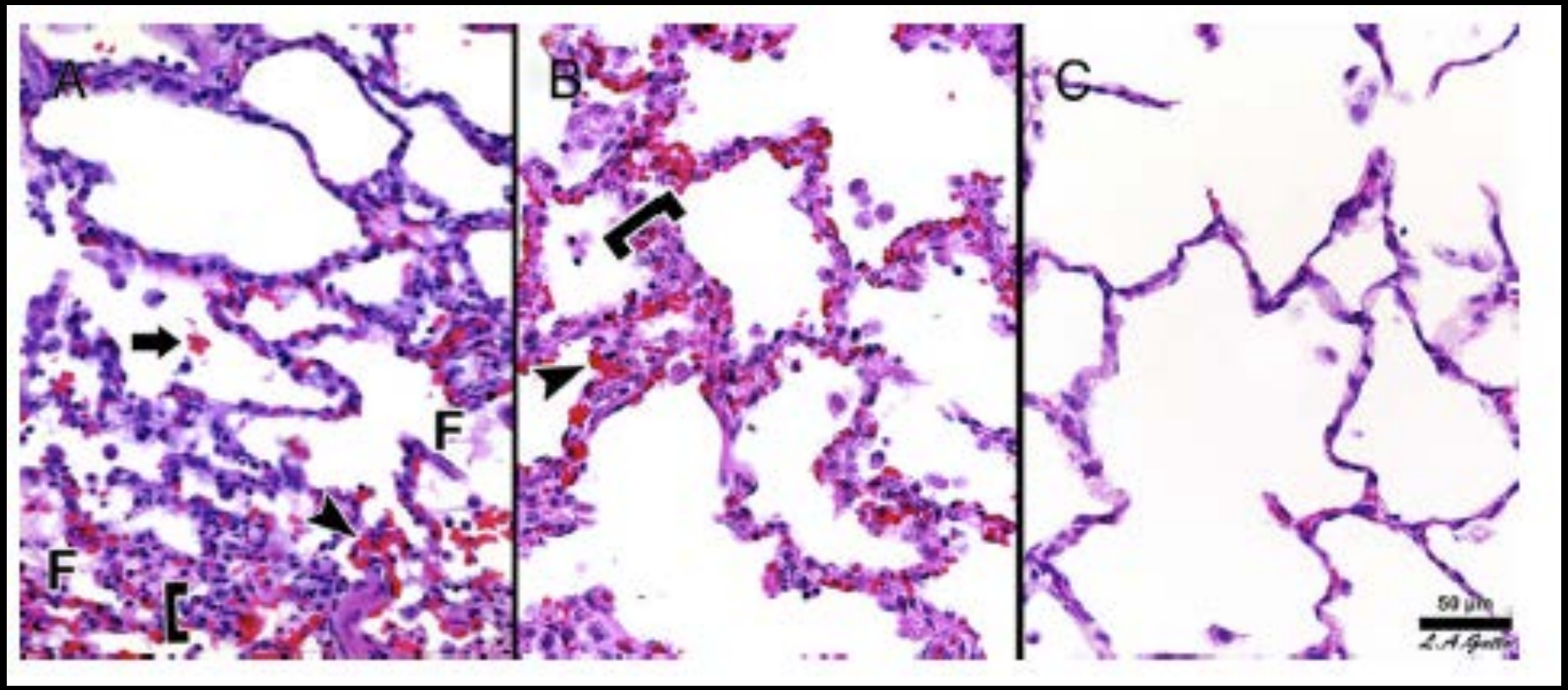


Roy et al *Shock* 2013;39: 28

UPSTATE
MEDICAL UNIVERSITY

Histopathology

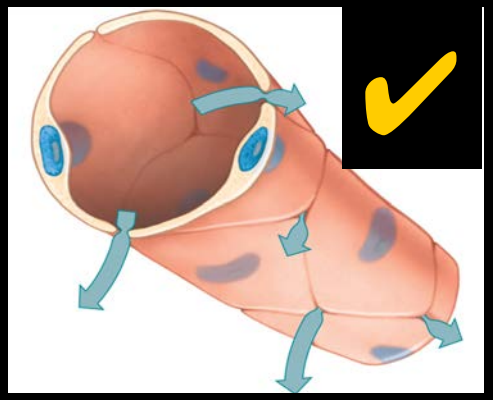
Sham ARDSnet APRV



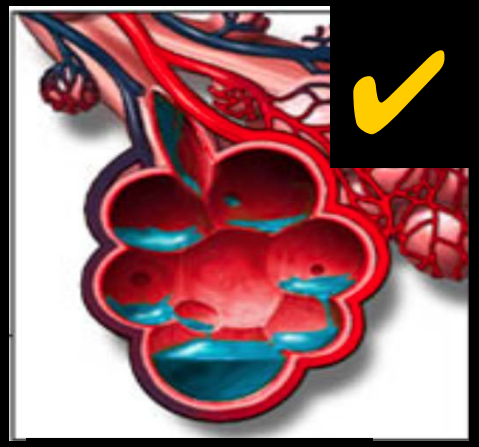
Roy et al *Shock* 2013;39: 28

UPSTATE MEDICAL UNIVERSITY

Conclusion: APRV inhibits the Tetrad of ARDS

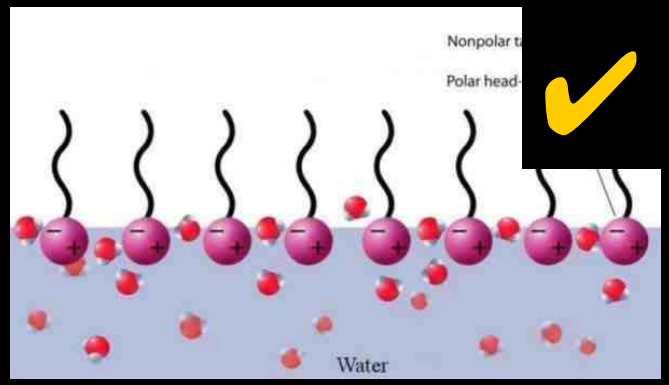


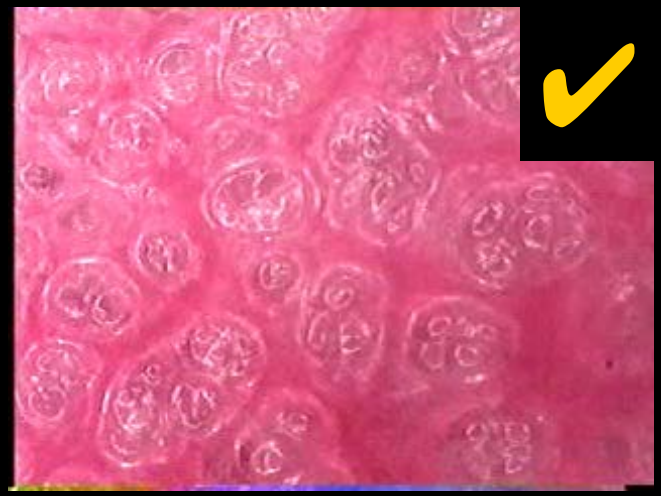
Appropriate P/T_P



Increased Capillary Permeability

Alveolar Edema





Alveolar Instability

Surfactant Deactivation

UPSTATE
MEDICAL UNIVERSITY

End of Experiment Ventilator Settings

ARDSnet n=4

Tidal Volume/kg	**5.77 ± 0.38**
PEEP	**20 ± 2.31**
FiO2	**0.73 ± 0.15**

APRV n=4

Tidal Volume/kg	**11.98 ± 0.77**
Thigh	**5.30 ± 0.76**
Tlow	**0.48 ± 0.03**
Phigh	**31.00 ± 3.51**
Plow	**0.0 ± 0.0**
FiO2	**0.21 ± 0.0**

Roy et al *Shock* 2013;39: 28

UPSTATE
MEDICAL UNIVERSITY

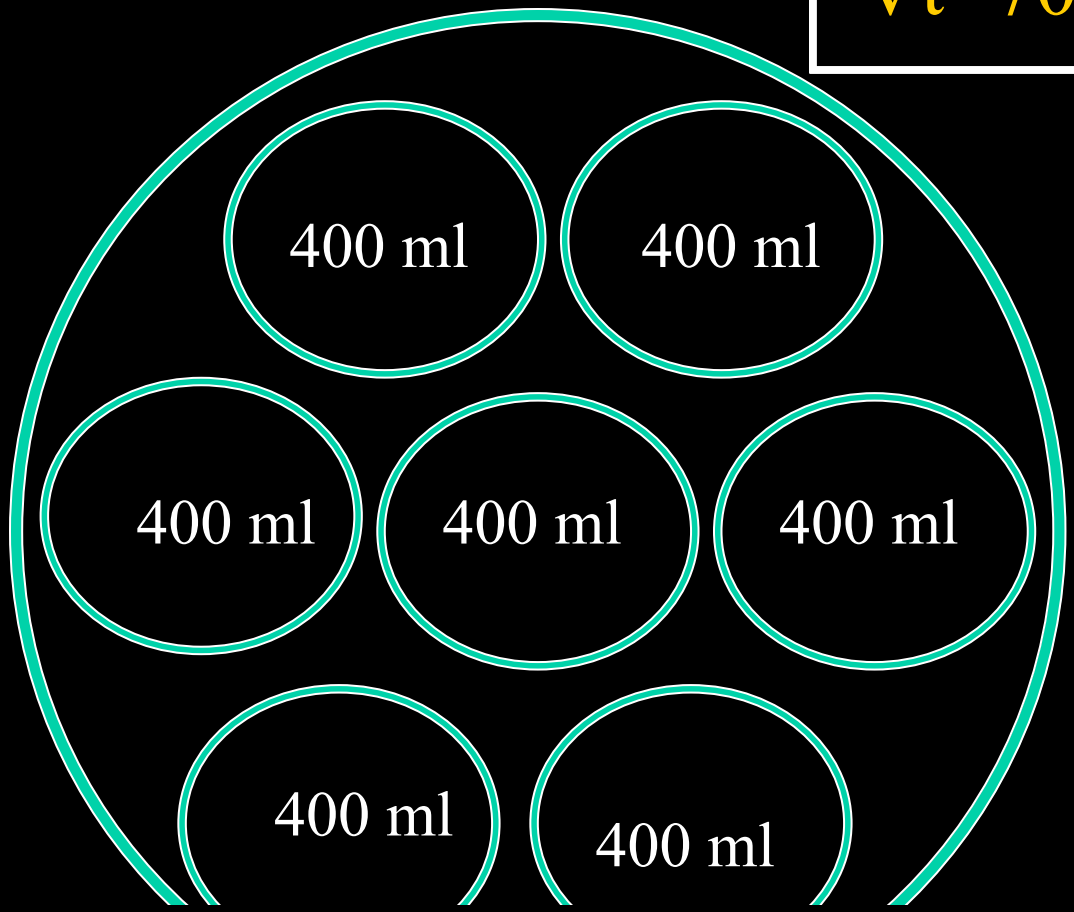
Micro-Anatomical Environment

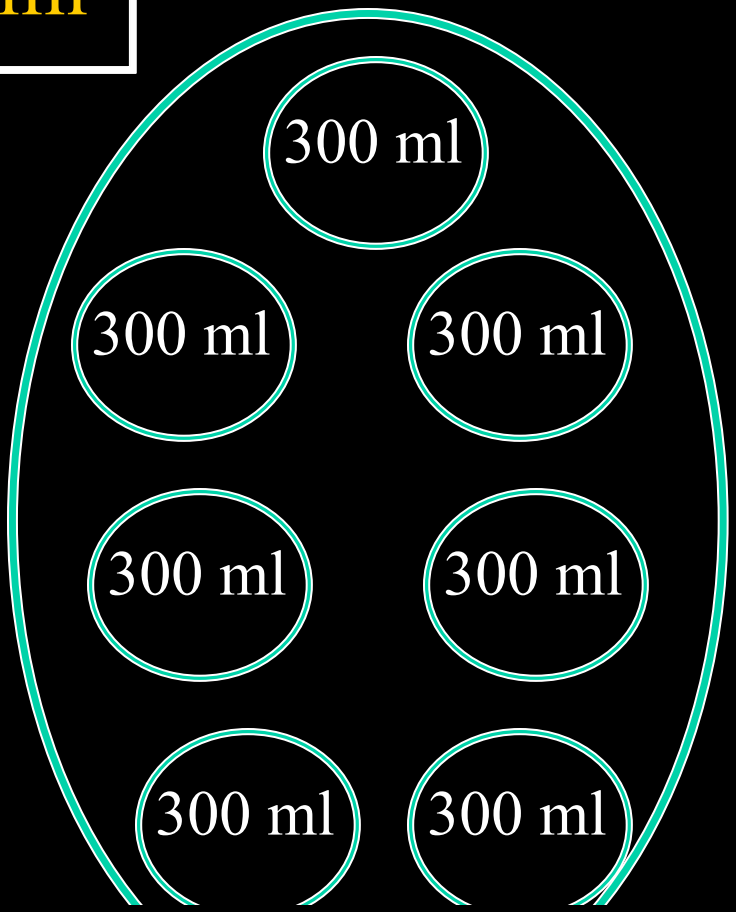
- Tracheal Tidal Volume (tV_t)
  - V_t delivered by the ventilator to the trachea
- Alveolar Tidal Volume (aV_t)
  - The portion of tV_t delivered to each individual alveoli
- The critical physiologic factor in the development of VILI is not the size of tV_t, but how this tV_t impacts ΔaV_t

UPSTATE
MEDICAL UNIVERSITY

Ventilation Near TLC

Vt=700ml





Each Alveolus as to change volume 25%

Inspiration

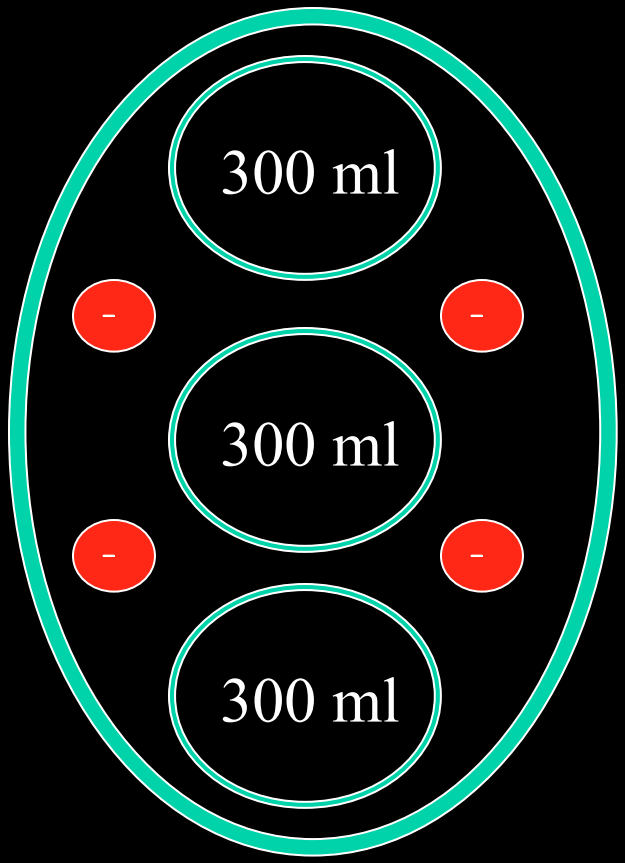
Expiration

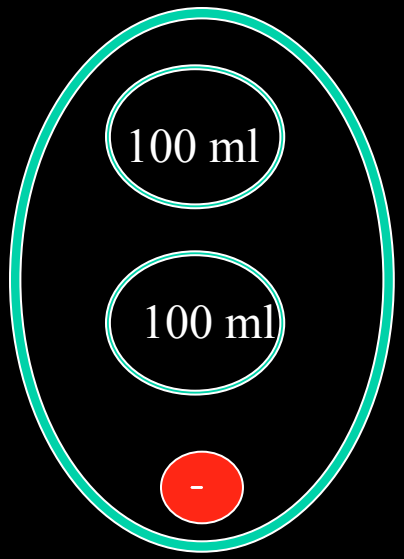
UPSTATE MEDICAL UNIVERSITY

Ventilation Near FRC

Vt=700ml

- = Collapsed Alveoli





Two Alveoli change volume 66% and the other changes 100%

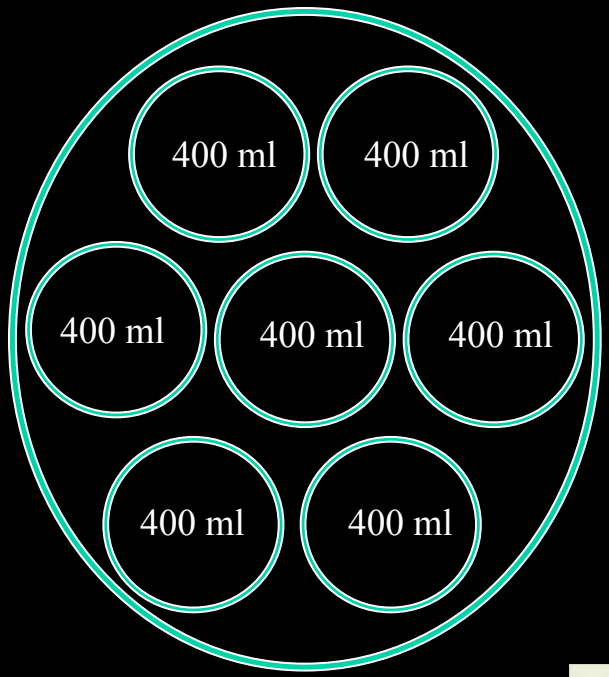
Inspiration

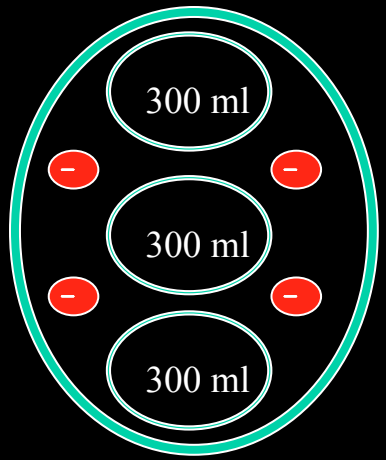
Expiration

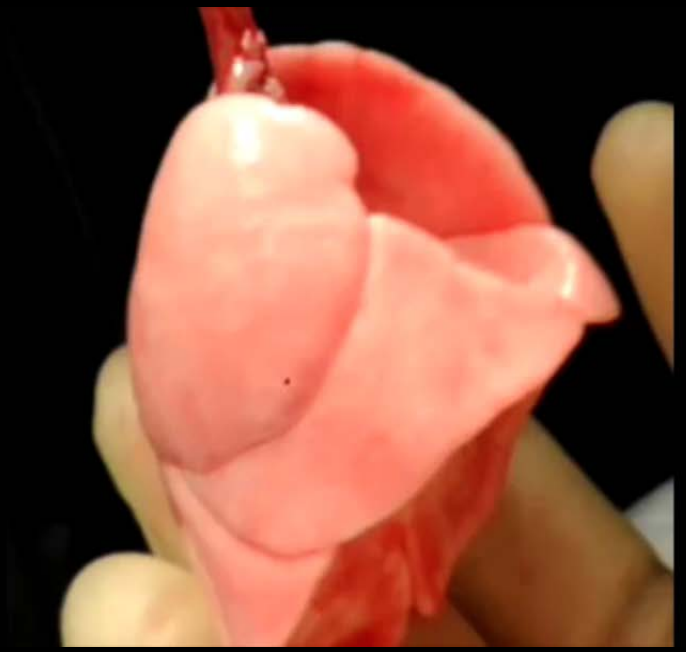
UPSTATE MEDICAL UNIVERSITY

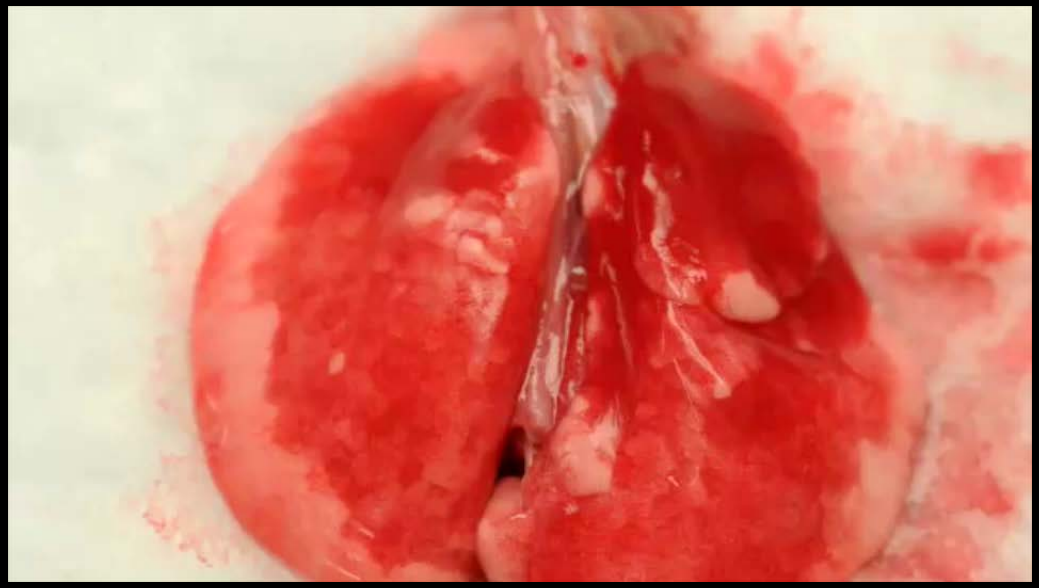
Micro-Anatomical Environment

Vt 700



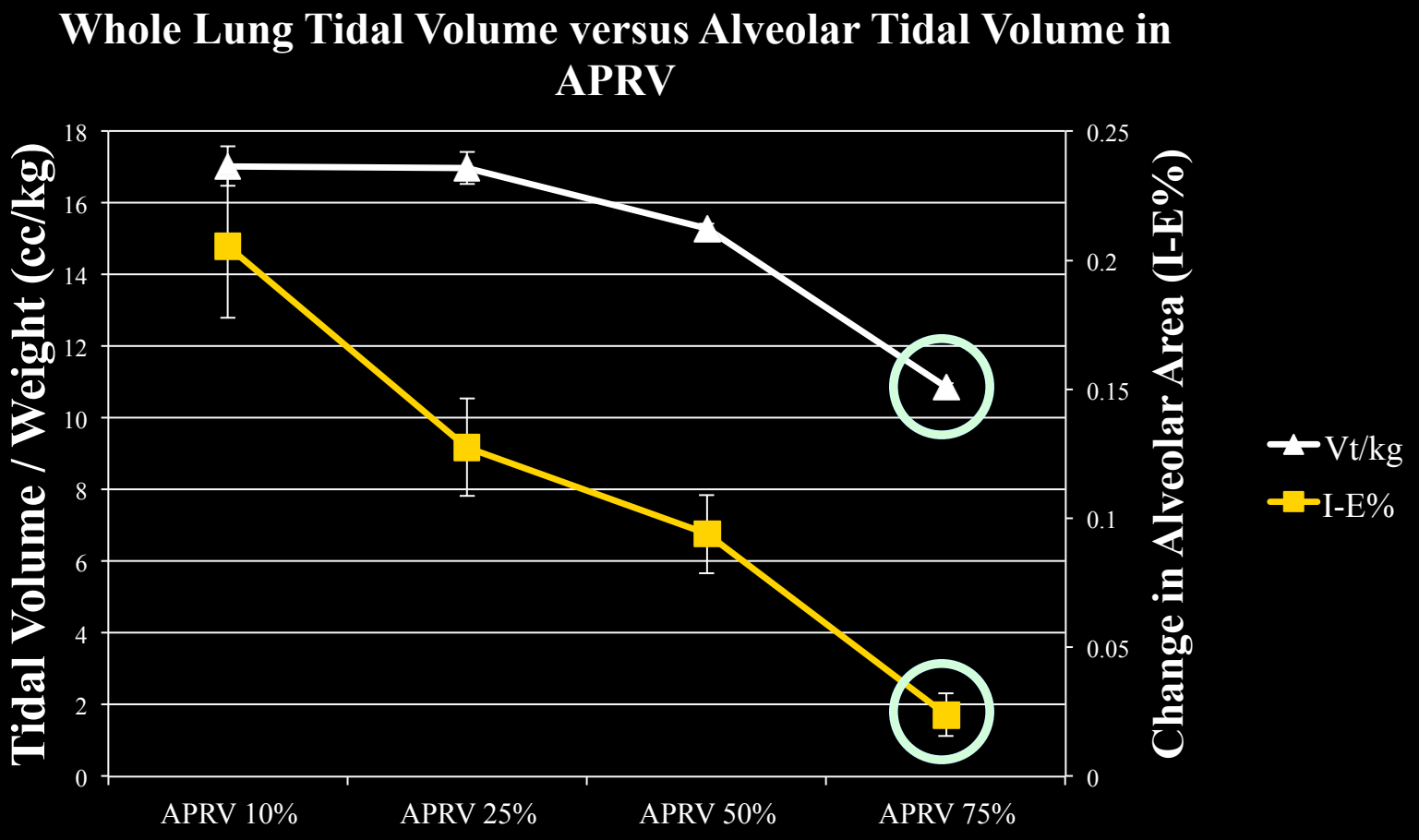






UPSTATE
MEDICAL UNIVERSITY

Micro-Anatomical Environment



UPSTATE
MEDICAL UNIVERSITY

It is not just the absolute size of the tidal volume but rather the size of the tidal volume in relation to volume of the lung being ventilated

UPSTATE
MEDICAL UNIVERSITY

Take an Entirely New Approach

- Deconstruct the mechanical breath
  - Analyze all 10 components of the mechanical breath (pressures, flows, rates, volumes, *Times*)
  - Mechanical Breath Profile (MB_P)

- Determine the impact of any given MB_P on the Micro-environment – the alveoli and alveolar ducts

UPSTATE
MEDICAL UNIVERSITY

Impact of the MB_P

Micro-environment

Alveoli and Alveolar Ducts

UPSTATE
MEDICAL UNIVERSITY

Research

Original Investigation | ASSOCIATION OF VA SURGEONS

Mechanical Breath Profile of Airway Pressure Release Ventilation

The Effect on Alveolar Recruitment and Microstrain in Acute Lung Injury

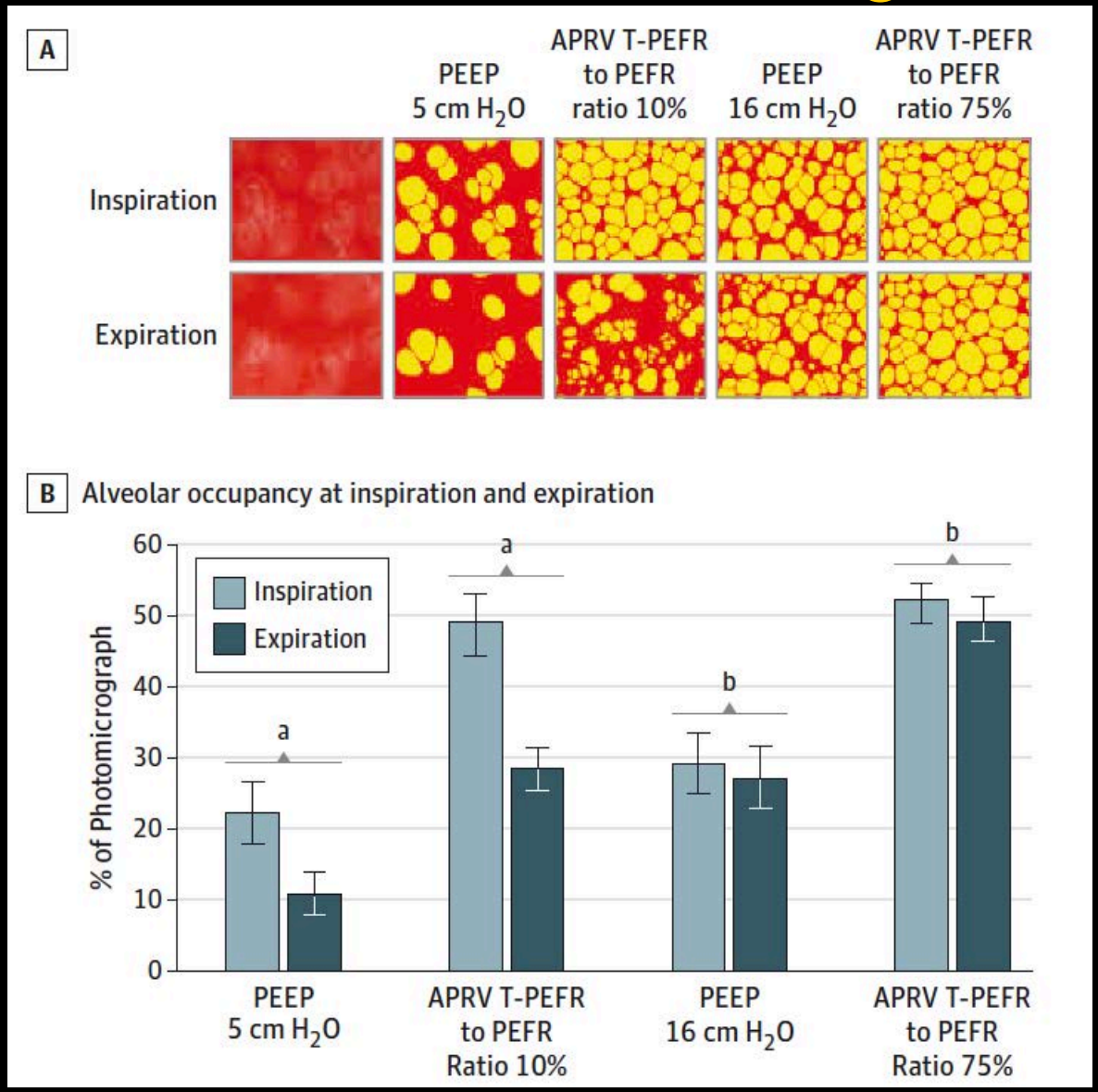
Michaela Kollisch-Singule, MD; Bryanna Emr, MD; Bradford Smith, PhD; Shreyas Roy, MD; Sumeet Jain, MD; Joshua Satalin, BS; Kathy Snyder; Penny Andrews, RN; Nader Habashi, MD; Jason Bates, PhD; William Marx, DO; Gary Nieman, BA; Louis A. Gatto, PhD

Kollish-Singule M, *JAMA Surgery*, In Press

UPSTATE
MEDICAL UNIVERSITY

Kollish-Singule M, *JAMA Surgery*, In Press

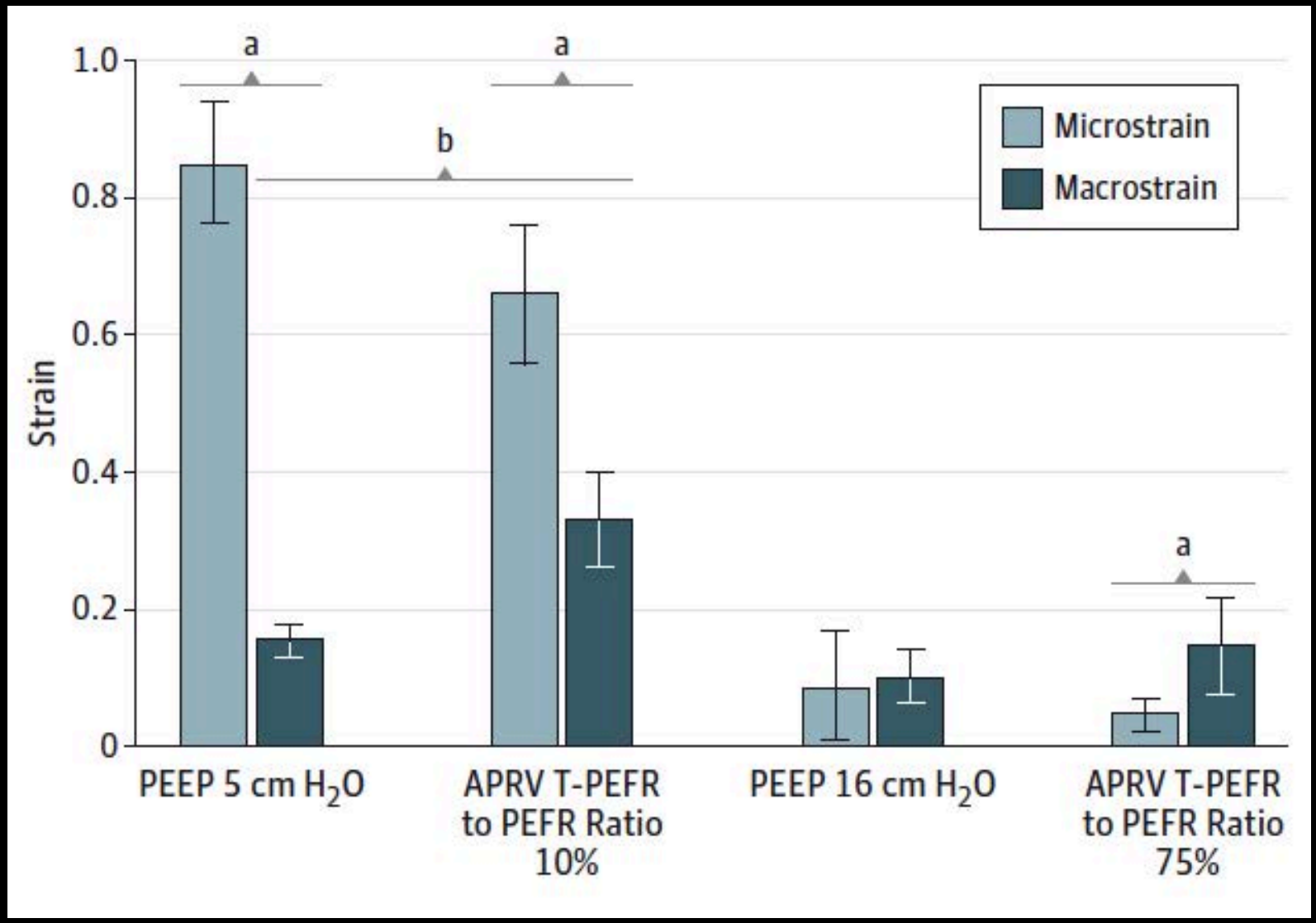
Dynamic Alveolar Strain during Ventilation



UPSTATE
MEDICAL UNIVERSITY

Kollish-Singule M, *JAMA Surgery*, In Press

Macro- vs Micro-Strain



UPSTATE
MEDICAL UNIVERSITY

Conclusions

- APRV 75% both recruits and stabilizes alveoli, preventing collapse during expiration
- APRV 75% minimizes alveolar micro-strain

UPSTATE
MEDICAL UNIVERSITY

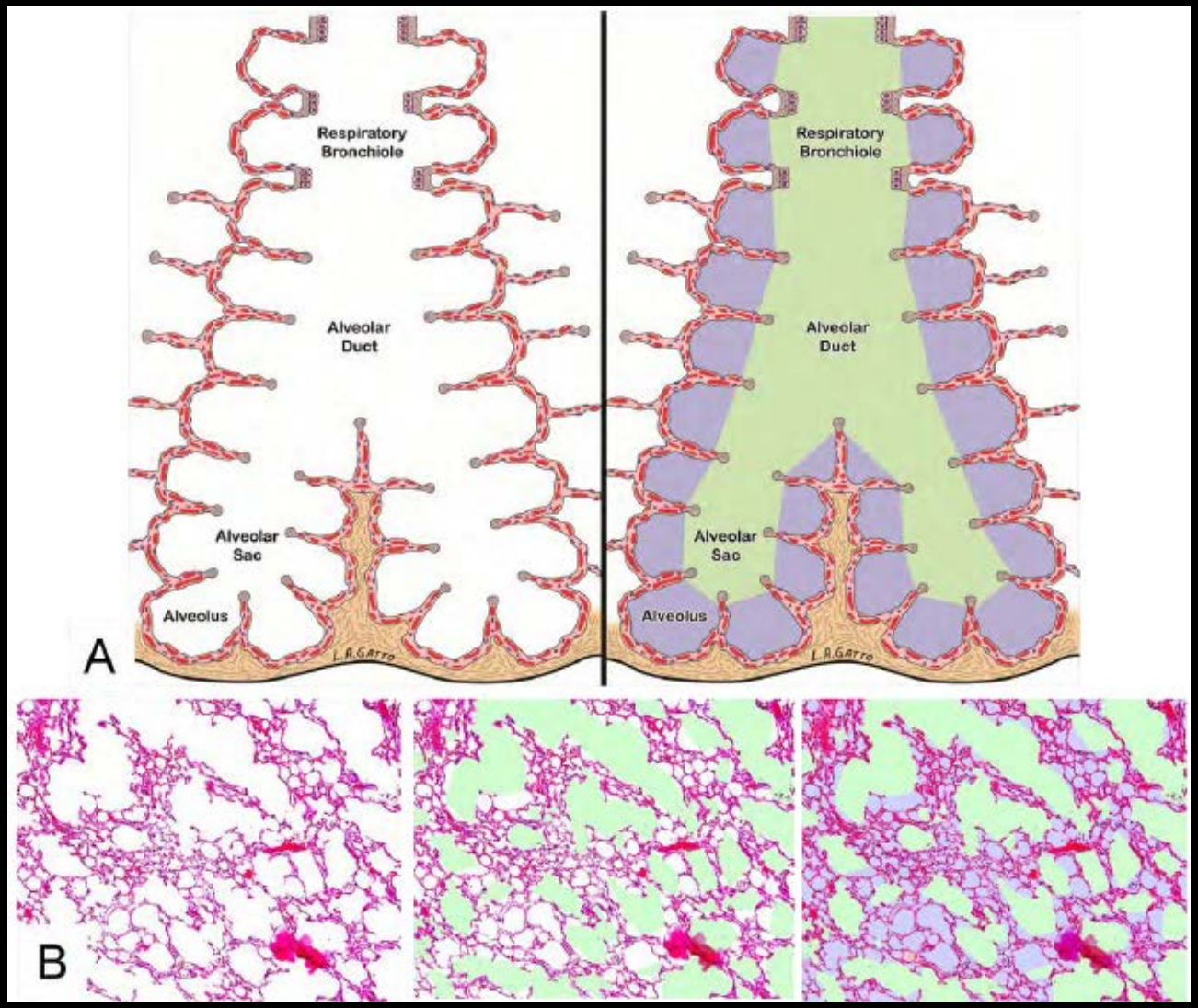
Kollish-Singule M, *J Am College Surgeons*, In Press

"Airway Pressure Release Ventilation (APRV) Reduces Conducting Airway micro-Strain in Lung Injury"

UPSTATE
MEDICAL UNIVERSITY

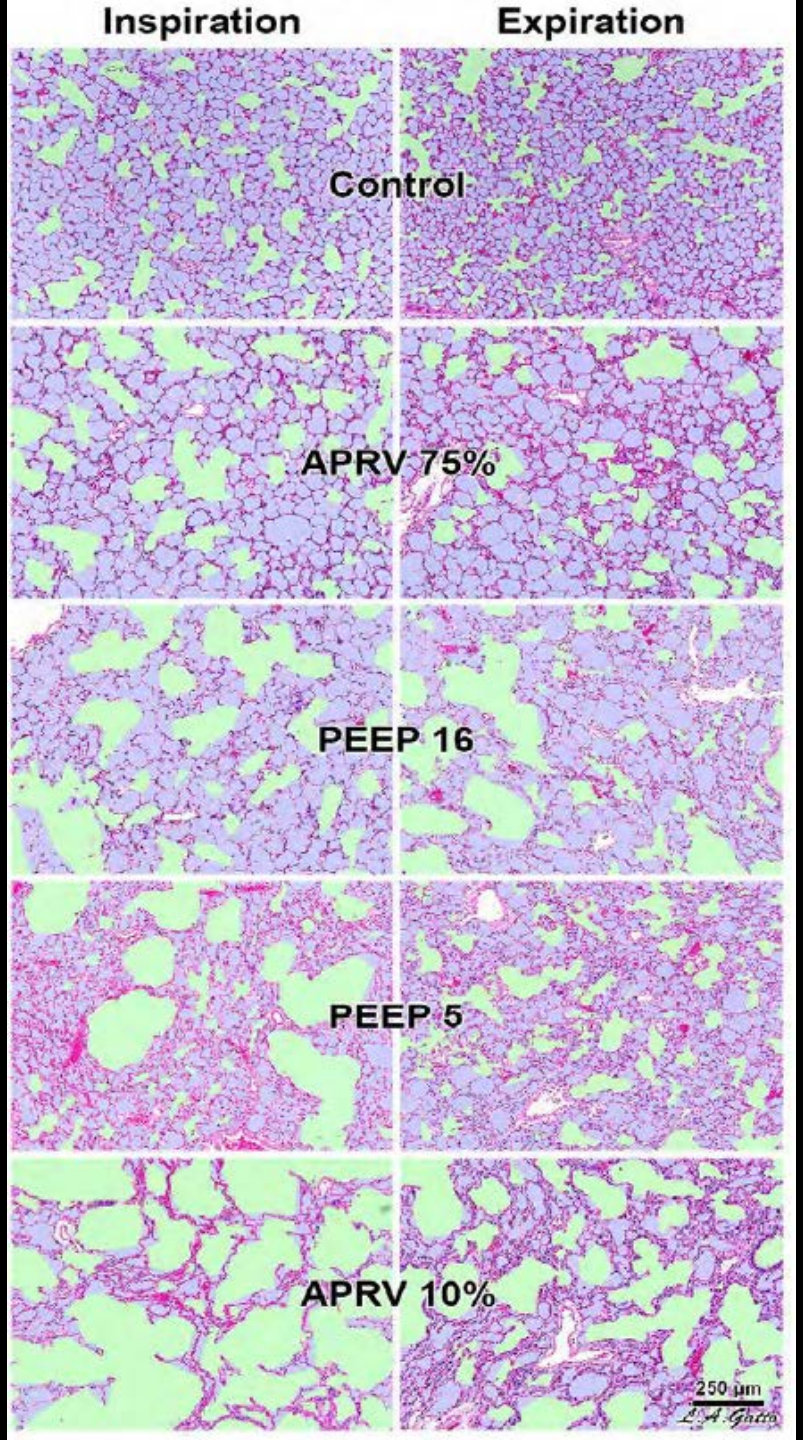
Kollish-Singule M, *J Am College Surgeons*, In Press

Schematic of the Terminal Airway



UPSTATE
MEDICAL UNIVERSITY

ARDS Lungs
MV

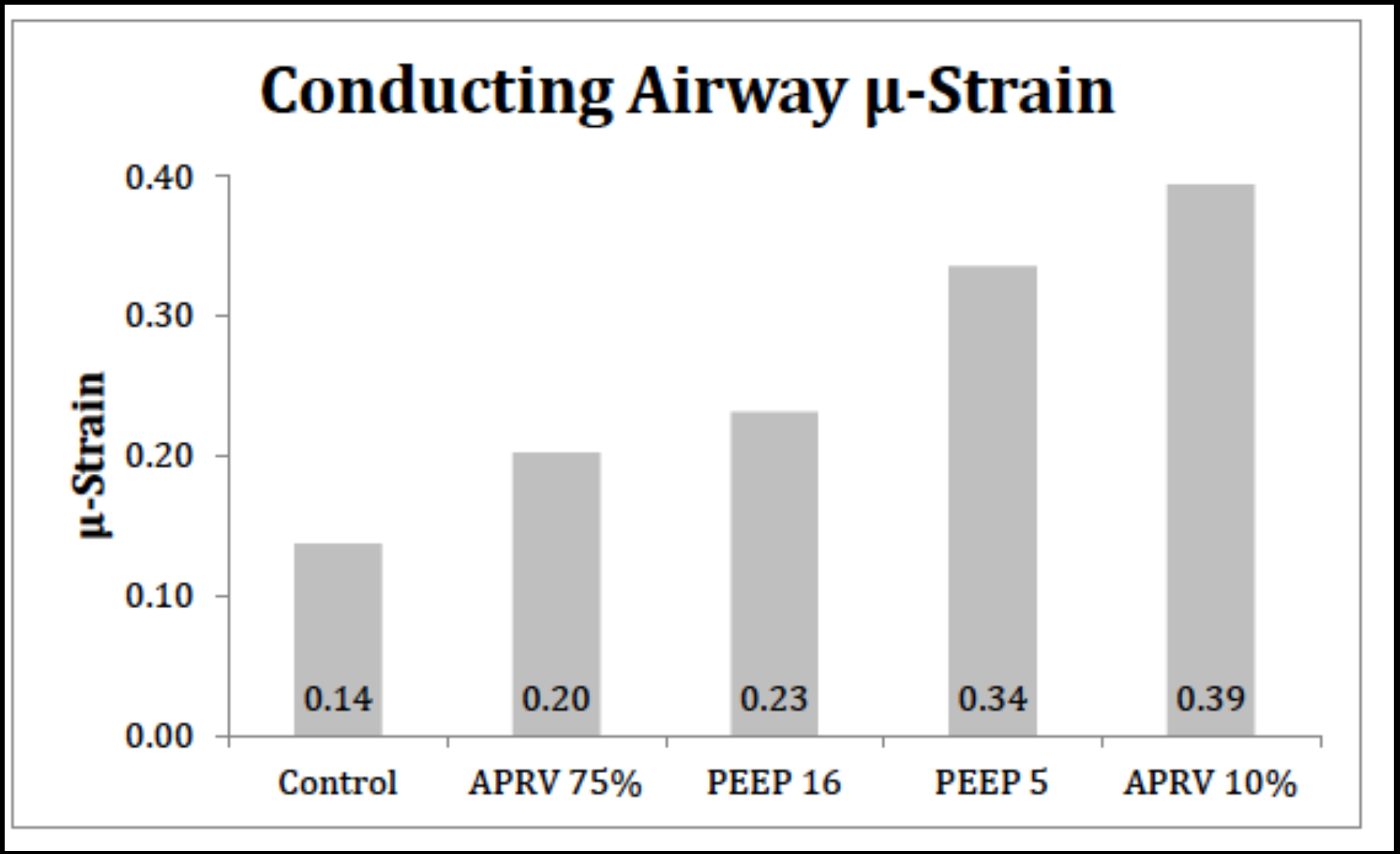


Normal Lung - SB

Kollish-Singule M, *J Am College Surgeons*, In Press

UPSTATE
MEDICAL UNIVERSITY

Kollish-Singule M, *J Am College Surgeons*, In Press



UPSTATE
MEDICAL UNIVERSITY

Conclusions

- The volume of gas in the conducting airways (i.e. ducts) was increased in all lung injured groups.
  - This shift was minimized with APRV 75%
- The volume of gas in the alveoli was reduced in all lung injured groups
  - This shift was minimized with APRV 75%
- Conducting airway micro-strain was minimized with APRV 75%

UPSTATE
MEDICAL UNIVERSITY

Lecture Summary

- ARDS is a progressive disease similar to cancer
- Most ARDS develops in the hospital so there is a window of prevention
- Clinical studies have shown that preemptive application of low Vt ventilation to patients with normal lungs, but at high risk, reduces ARDS incidence
- Mechanical injury to the pulmonary parenchyma with inappropriately set mechanical ventilation is a key mechanism driving progressive acute lung injury

UPSTATE
MEDICAL UNIVERSITY

Lecture Summary

- In order to scientifically determine how to reduce the mechanical injury caused by MV we must know:
  - The pathologic impact of mechanical injury
  - What components in the mechanical breath (MB_P) are harmful or protective
  - How does any given MB_P impact the Terminal Airway

- We have found that the *Time* pressures and volumes are applied to the lung during each breath are critical for lung protection

- Multiple studies from our lab have shown that preemptive application of appropriately set APRV will block progressive lung damage and prevent ARDS in animals at very high risk

UPSTATE
MEDICAL UNIVERSITY

Conclusion

"ARDS is no longer a syndrome that must be treated, but is a syndrome that should be prevented."

Villar and Slutsky *Critical care.* 2010;14(1):120.

UPSTATE
MEDICAL UNIVERSITY

Can the Ventilator be used as a Drug to Prevent ARDS?

Preemptive Ventilation

Waiting for Established-ARDS

UPSTATE
MEDICAL UNIVERSITY

Therapeutic Use of Mechanical Ventilation: Can We Change the Way We Manage the Patient?

2014 Suncoast Pulmonary Symposium
Hyatt Regency Coconut Point Resort
Bonita Springs, Florida
September 10-12, 2014

Gary F. Nieman

Associate Professor

Department of Surgery

Director,

Cardiopulmonary and Critical Care Laboratory

SUNY Upstate Medical University

Syracuse, NY

Niemang@upstate.edu

UPSTATE
MEDICAL UNIVERSITY