CALIFORNIA THORACIC SOCIETY
ANNUAL EDUCATIONAL CONFERENCE

FRIDAY, JANUARY 18, 2019

ARDS: ADVANCED STRATEGIES IN VENTILATOR MANAGEMENT

REGISTRATION/EXHIBITS

Friday, January 18, 2019 – 7:00 a.m. – 8:00 a.m.

PROGRAM SCHEDULE

FRIDAY, JANUARY 18, 2019

ARDS: ADVANCED STRATEGIES IN VENTILATOR MANAGEMENT

7:00 am – 8:00 am
Registration / Exhibits

8:00 am – 8:05 am
Welcome and Introductions; Pre-Test
William Stringer, MD; George Su, MD

8:05 am – 8:55 am
KEY NOTE SPEAKER: The Acute Respiratory Distress Syndrome (ARDS)
Michael Matthey, MD

8:55 am – 9:45 am
Advances in Ventilator Management of ARDS
Angela Rogers, MD

9:45 am – 10:00 am
BREAK / EXHIBIT HALL OPEN

10:00 am – 10:45 am
Driving Pressure and Lung Mechanics
Atul Malhotra, MD

10:45 am – 11:35 am
Refractory Hypoxemia
Joseph Levitt, MD, MS

11:35 am – 12:05 pm
LARGE GROUP: (Audience Response): Ventilator Management 1: Ventilator Graphics, Scalars, Lung Mechanics (ASL 5000 with vent)
Lance Pangilinan, RRT; Justin Phillips, RRT; Gregory Burns, RRT; Vivian Yip, RRT; Rich Kallet, MS, RRT

12:05 pm – 1:10 pm
LUNCH / EXHIBIT HALL OPEN

1:10 pm – 1:55 pm
Consequences of Unintended Intubation
Neil Ross MacIntyre, MD

1:55 pm – 2:40 pm
ARDS, Respiratory Failure and Blood Biomarkers
Angela Rogers, MD

2:40 pm – 3:00 pm
BREAK / EXHIBIT HALL OPEN

3:00 pm – 3:45 pm
New Strategies in Aerosolized Therapies in Critical Care
Jim Fink, PhD

3:45 pm – 4:30 pm
LARGE GROUP: (Audience Response): Ventilator Management 2: Case Examples in ARDS and Respiratory Failure
Lance Pangilinan, RRT; Justin Phillips, RRT; Gregory Burns, RRT; Vivian Yip, RRT; Rich Kallet, MS, RRT

4:30 pm – 5:15 pm
Prone Positioning, Recruitment maneuvers
Rich Kallet, MS, RRT

5:15 pm - 5:20 pm
Closing Remarks and Post Test
William Stringer, MD; George Su, MD

WELCOME AND INTRODUCTIONS
PRE-TEST

William Stringer, MD, FACP, FCCP
Professor of Medicine
David Geffen School of Medicine at UCLA
Attending Physician
Harbor-UCLA Medical Center

George Su, MD
Associate Professor of Medicine
UC San Francisco
Zuckerberg San Francisco General Hospital

Friday, January 18, 2019 – 8:00 a.m. – 8:05 a.m.

THE ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS)

Michael Matthay, MD
UC San Francisco
Professor of Medicine and Anesthesia

Friday, January 18, 2019 – 8:05 a.m. – 8:55 a.m.

Michael A. Matthay, MD is a Professor of Medicine and Anesthesia at the University of California at San Francisco and a Senior Associate at the Cardiovascular Research Institute. He is Associate Director of the Intensive Care Unit. He received his AB from Harvard University and his MD from the University of Pennsylvania School of Medicine. He received an American Thoracic Society award for Scientific Achievement in 2002 and the UCSF Award for Outstanding Clinical Research in 2006, as well as the Lifetime Achievement Award in Mentoring at UCSF in 2013. He is a member of the American Association of Physicians.

Research Interests: Dr. Matthay's basic research has focused on mechanisms of salt, water, and protein transport across the alveolar epithelium that account for the resolution of pulmonary edema. He has also studied the pathogenesis and resolution of pulmonary edema and the acute respiratory distress syndrome (ARDS). His recent research has also focused on the biology and potential clinical use of allogeneic bone marrow derived mesenchymal stromal (stem) cells for ARDS.

Acute Respiratory Distress Syndrome 1967-2019 What Have We Learned?

Disclosures

- Grant support for lab-based and clinical research from NHLBI (R01, R35, R42, U54)
- Grant support for Clinical Trials (NHLBI-U01 and Dept of Defense)
- Grant support for Cell-Therapy Network (Alpha Stem Cell Clinic – California Institute of Regenerative Medicine)
- Grant support for observational study of Pulmonary Hypertension and ARDS (Bayer)
- No conflicts for this presentation

The Lancet · Saturday 12 August 1967

ACUTE RESPIRATORY DISTRESS IN ADULTS

DAVID G. ASHBAUGH
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M.D. Colorado
ASSISTANT IN MEDICINE AND AMERICAN THORACIC SOCIETY-NATIONAL TUBERCULOSIS ASSOCIATION FELLOW IN PULMONARY DISEASE

THOMAS L. PETTY
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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.

"The clinical pattern, which we will refer to as the respiratory-distress syndrome, includes

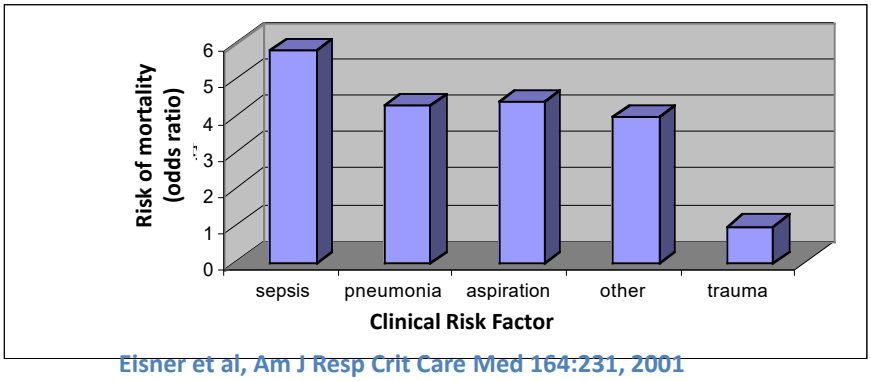
- severe dyspnea
- tachypnea
- cyanosis that is refractory to oxygen therapy
- loss of lung compliance
- diffuse alveolar infiltration seen on CXR"

12 patients (7 trauma, 4 viral infection, 1 pancreatitis)

Our Understanding of ARDS has Evolved

- **Prognosis, Definitions & Pathology**
- **Epidemiology**
- **Pathophysiology & Modified Lung Injury Score**
- **Pathogenesis**
- **Impact of clinical trials**
- **Treatment – timing & the routes for therapeutic interventions**

Mortality Risk in ARDS Depends on the Clinical Risk Factor Factors

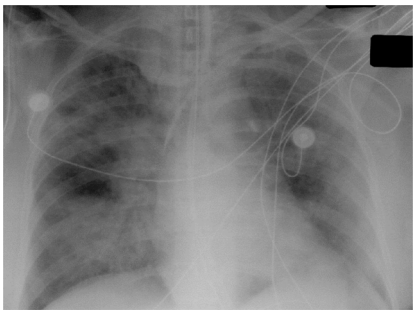


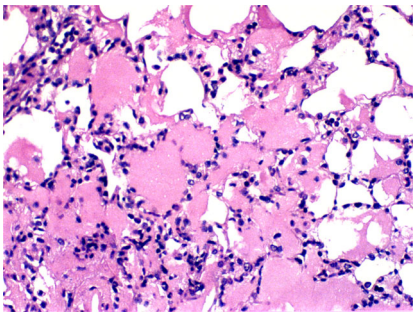
Eisner et al, Am J Resp Crit Care Med 164:231, 2001

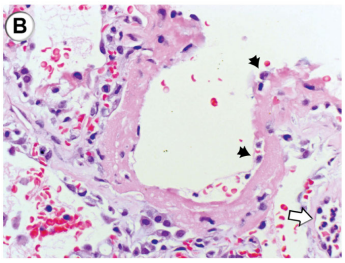
Berlin Definition of ARDS – JAMA 2012

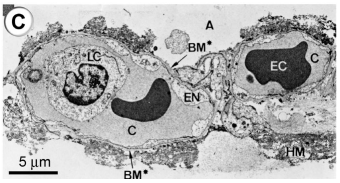
- **Timing**: Respiratory failure within 1 week of a known insult or new/worsening respiratory symptoms
- **Imaging**: Bilateral opacities on chest radiograph or CT not fully explained by effusion, collapse or nodules
- **Origin:** Respiratory failure not fully explained by cardiac function or volume overload (objective criteria such as echocardiography to exclude hydrostatic edema if no risk factor is present)
- **Oxygenation: acute onset of hypoxemia defined as PaO_2/FiO_2 <300 mmHg on at least PEEP 5 cmH_2O***
  - PaO_2/FiO_2 of 201-300 mmHg is mild ARDS
  - PaO_2/FiO_2 of 101-200 mmHg is moderate ARDS
  - PaO_2/FiO_2 ≤100 mmHg is severe ARDS

The Acute Respiratory Distress Syndrome (ARDS)

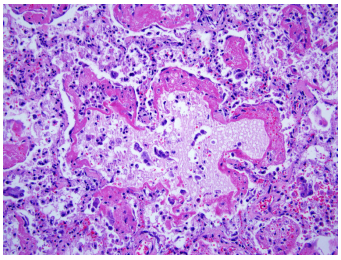


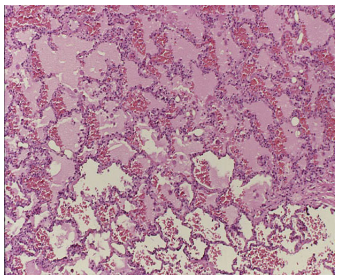






ARDS Pathology - 2019





- Classic pathology - diffuse alveolar damage (DAD) for patients with ARDS (Bachofen & Weibel, *ARRD*, 1997)
- However, ARDS pathology reveals diffuse alveolar damage in 45% of post-mortem Lung samples in patients who met the Berlin Criteria for ARDS 1991-2010 (Thille, *AJRCCM*, 2013)
- Also the incidence of diffuse alveolar damage declined in the decade after institution of lung protective ventilation

Int Care Med, 2016

Epidemiology of ARDS in 2019
(Incidence & Prevalence)

- Incidence 200,000 annually in the US (NEJM, 2005) from 21 hospitals in Kings County in Washington
- SF Bay Area study at UCSF and Oakland Childrens' hospitals identified 328 children with ARDS over 4 years (AJRCCM, 2005)
- International study – SAFE – Winter of 2014 - in 50 countries in cross-sectional analysis of 29,144 patients - 10% of ICU patients had ARDS by Berlin Definition with 23% incidence in ventilated patients (JAMA 2016).

Epidemiology of ARDS in 2019
(Mortality & Clinical Recognition, SAFE study)

- Mortality in the SAFE study – 35% mild ARDS; 40% for moderate ARDS; 46% for severe ARDS (*JAMA* 2016)
- Mortality attributable to ARDS itself versus associated comorbidities and chronic diseases not clear although mortality higher in immunocompromised subgroup
- Clinical recognition of ARDS was low at 51% in mild ARDS and 79% in severe ARDS in the SAFE study (*JAMA* 2016)
- Less than 2/3 of patients treated with lung protective ventilation with tidal volume < 8 ml/kg tidal volume predicted body weight
- ARDS common but under-recognized and under-treated

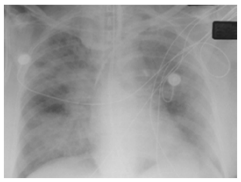
Epidemiology of ARDS in 2019
(Trauma, TRALI, Environmental Factors)

- Trauma related ARDS – incidence markedly reduced, perhaps secondary to reduction in use of crystalloid for resuscitation (*J Trauma Acute Care Surg* 2013)
- Cigarette use, alcohol abuse and air pollution associated with higher incidence of ARDS (*AJRCCM*, 2015;2016)
- TRALI lower incidence since exclusion of female donors for fresh frozen plasma (*Blood*, 2014)
- In-hospital ARDS reduced in incidence over 8 years, probably related to reduced use of blood products, less nosocomial pneumonia, and reduced use of higher tidal volumes in the OR and the ICU (*AJRCCM,* 2011)

Epidemiology of ARDS in 2019
(Genetic Factors)

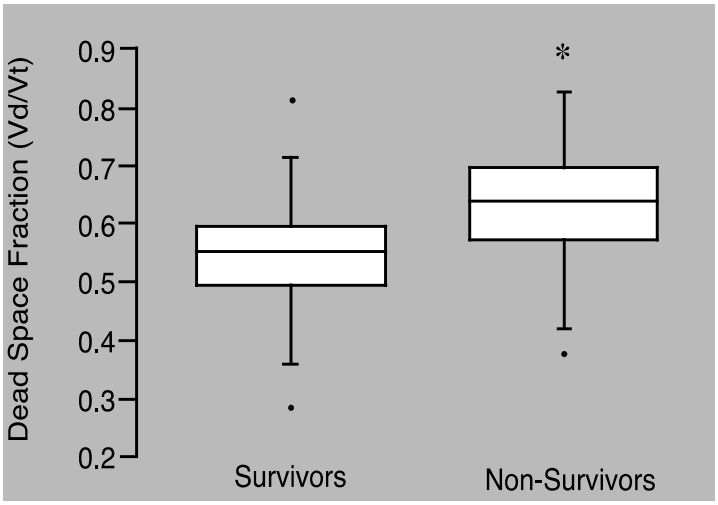
- Higher mortality for Hispanic and African American patients with ARDS though (*Crit Care Med*, 2009) and higher mortality in men than women with ARDS though mechanisms for these differences not well worked out yet
- Some genetic factors associated with risk for developing ARDS by GWAS not achieved at genome wide level for significance
- But candidate gene and pathway analyses revealed some potential contributors, such as ANGPT2 genetic variants in European ancestry that code for angiopoietin-2, mediator and marker of vascular injury *(Int Care Med*, 2018)

Pathophysiology of ARDS – What Have We Learned?



- Hypoxemia is the classic physiologic abnormality in ARDS, explained by alveolar edema and alveolar collapse, with low ventilation to perfusion lung units and intra-pulmonary shunting.
- However, in almost all ARDS trials the minute ventilation is twice normal (12 versus 6 liters per minute). Why?
- Either there is marked increase in carbon dioxide production or there is an increase in alveolar dead space (high ventilation to perfusion lung units).
- So we did a prospective study of 179 patients at SFGH and UCSF Parnassus over 3 years of early ARDS (first 24 hours)

Dead Space and Mortality in Early ARDS



Pulmonary Dead Space Independently Predicts Mortality in Early ARDS

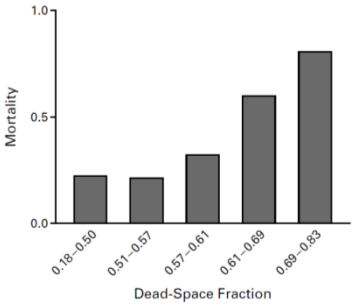


TABLE 3. ODDS RATIOS FOR VARIABLES INDEPENDENTLY ASSOCIATED WITH AN INCREASED RISK OF DEATH.*

VARIABLE	ODDS RATIO (95% CI)	P VALUE
Dead-space fraction (per increase of 0.05)†	1.45 (1.15–1.83)	0.002
SAPS II (per 1-point increase)	1.06 (1.03–1.08)	<0.001
Quasistatic respiratory compliance (per decrease of 1 ml/cm of water)	1.06 (1.01–1.10)	0.01

$$Vd/Vt = (PaCO_2 - P_ECO_2)/PaCO_2$$

Nuckton, T. J. *et al.* Pulmonary dead-space fraction as a risk factor for death in the acute respiratory distress syndrome. *N. Engl. J. Med.* **346,** 1281–1286 (2002).

Ventilatory Ratio (VR) Estimates Dead Space in ARDS and Independently Predicts Mortality

- **Physiological Analysis and Clinical Performance of Ventilatory Ratio in ARDS *Am J Resp Crit Care* Med, 2018, Pratik Sinha, Carolyn S Calfee, Jeremy Beitler, Neil Soni, Michael A Matthay, Kelly Ho and Richard H Kallet**
- $$VR = \frac{\dot{V}_{E\ measured} \; X \; Pa_{CO_2\ measured}}{\dot{V}_{E\ predicted} \; X \; Pa_{CO_2\ ideal}}$$
- $\dot{V}_{E\ predicted}$ is the predicted minute ventilation calculated as predicted body weight X 100 (mL/min), and $Pa_{CO_2\ ideal}$ is the expected arterial pressure of carbon dioxide in normal lungs if ventilated with the predicted minute ventilation. $Pa_{CO_2\ ideal}$ is set as 37.5 mmHg (5 kPa) for all patients.
- VR was an independent predictor of mortality in ARDS after adjusting for P/F, PEEP, and driving pressure in 520 ARDS patients at ZSFG (Kallet's cohort)

The Potential Value of Quantifying Pulmonary Edema

- In our 4 point acute lung injury score, the scoring for bilateral infiltrates is of limited value
- A more detailed scoring system for the extent of pulmonary edema could be used to guide and assess therapy in ARDS
- Potential to provide outcome measures and guide clinical understanding of severity of illness

The RALE Score

- **R**adiographic **A**ssessment of **L**ung **E**dema

Assigned number	% of quadrant with consolidation
0	Clear
1	0-25%
2	25-50%
3	50-75%
4	75-100%
Assigned number	**Infiltrate Density of Each Quadrant**
1	Hazy opacity
2	Moderate opacity
3	Dense opacity

- Total
  - Multiply the consolidation and density score of each quadrant (max = 12)
  - Sum all four quadrants (max = 48)

Calculating a RALE Score

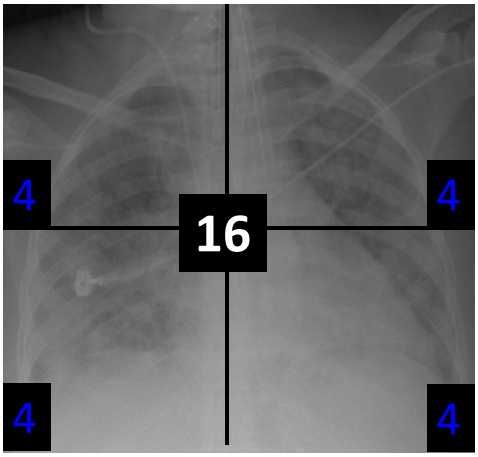


Figure 1A. Comparison of 2 CXR Scores

Score	RUL	RLL	LUL	LLL	Total
LIS	1	1	1	1	4
CONS	4	4	4	4	16

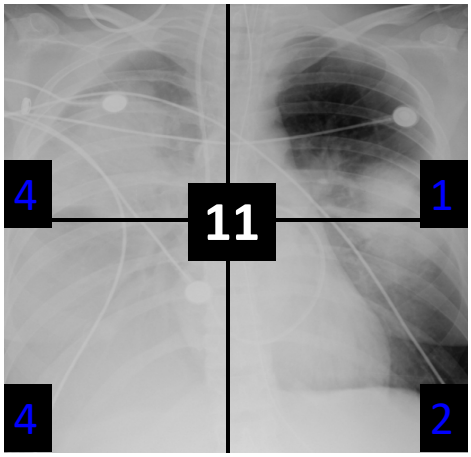


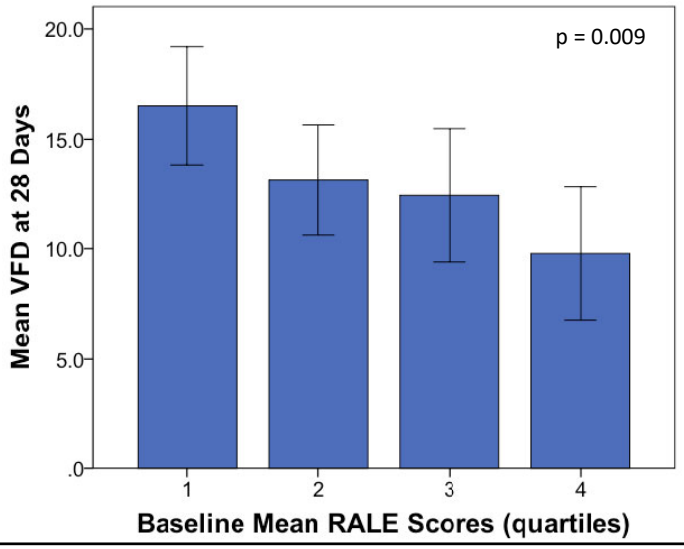
Figure 1B. Comparison of 2 CXR Scores

Score	RUL	RLL	LUL	LLL	Total
LIS	1	1	1	1	4
CONS	4	4	1	2	11

RALE Study Design

- 174 patients from FACTT
  - 5 centers: Baystate, Greensboro, San Francisco, Vanderbilt, Wake
  - 174 available baseline chest radiographs
  - 159 available follow-up Day 3 chest radiograph
  - Available clinical outcomes
    - Baseline and cumulative fluid balance
    - Baseline and delta P:F ratio
    - VFD
    - 28 and 60 day mortality
- Independently assigned each CXR a RALE score

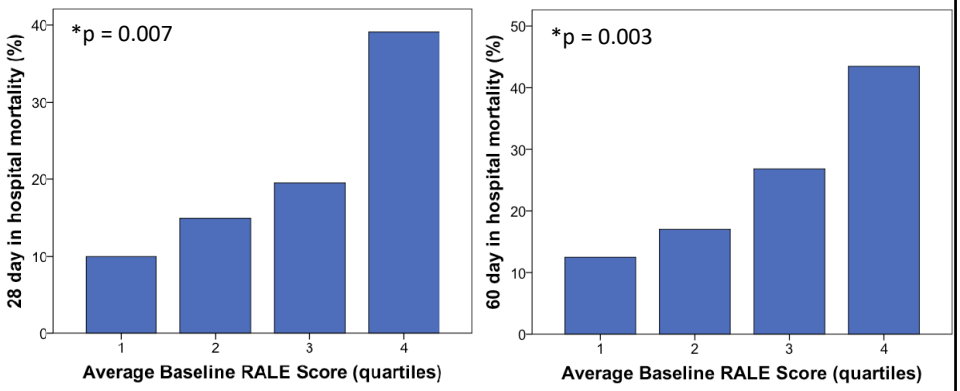
Average baseline RALE Score is associated with VFD at 28 days



Average baseline RALE Score is independently associated with VFD at 28 days

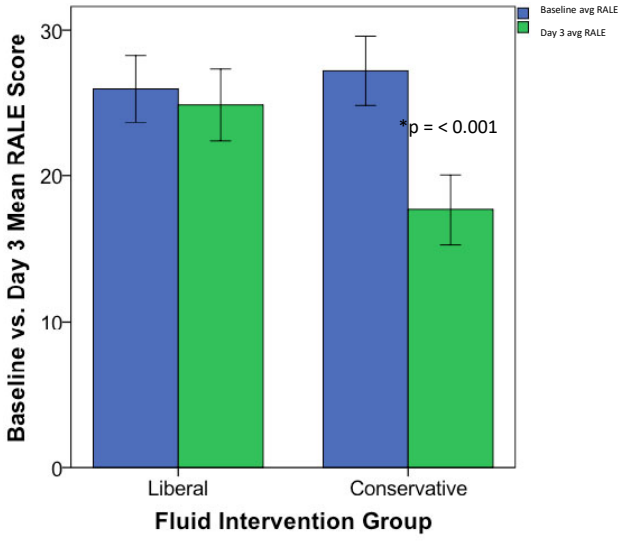
Predictors	Beta Coefficient	Confidence Interval	P value
Baseline mean RALE	-0.172	(-0.30, -0.01)	0.03
Age	-0.114	(-0.16, 0.02)	0.14
Gender	0.104	(-0.92, 4.80)	0.18
APACHE	-0.392	(-0.19, 0.78)	<0.001
BMI	-0.056	(-0.73, 0.47)	0.47
Etiology of ARDS (direct vs indirect)	-0.012	(-3.37, 2.92)	0.89
Baseline fluid balance	-0.045	(-0.45, 0.26)	0.58

Higher average baseline RALE Scores are associated with 28 and 60 day mortality



Warren et al, Thorax, 2018

Mean RALE Score decreases over time in conservative arm



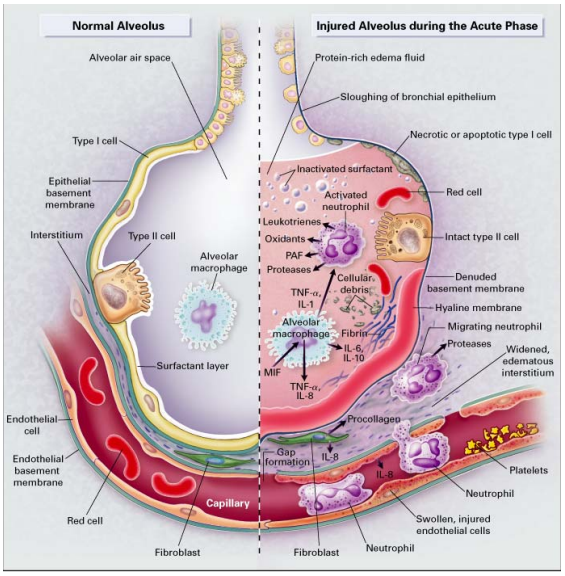
New Lung Injury Score for ARDS (probably still a 4-point score)

- Incorporate RALE score for extent of pulmonary edema
- Incorporate the Ventilatory Ratio to include measure of impaired $C0_2$ excretion
- Retain $Pa0_2/Fi0_2$ categories
- Retain the level of PEEP categories

(Compliance too difficult to include because unreliable data on plateau airway pressure)

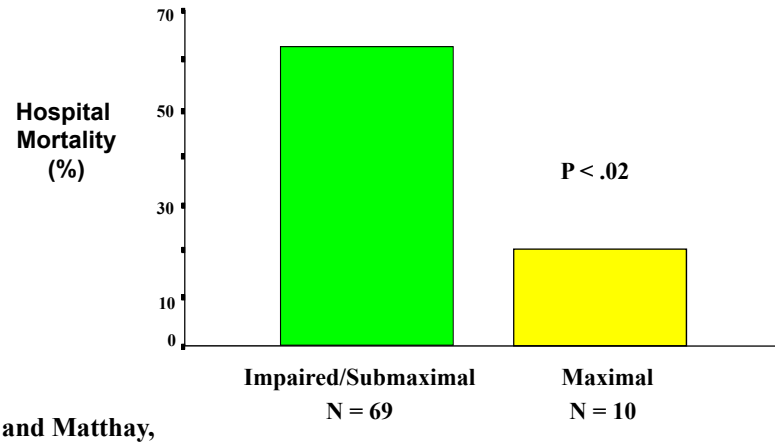
Pathogenesis of Acute Lung Injury – 2019 (Insights from Experimental & Clinical Studies)

- **Alveolar epithelial injury critical for severity of ARDS**
- **Role of neutrophil extracellular traps (NETs)**
- **Role of plasma cell-free hemoglobin**
- **How current effective therapies evolved from experimental studies**
- **Multiple factors combine to produce ARDS**



Ware & Matthay,

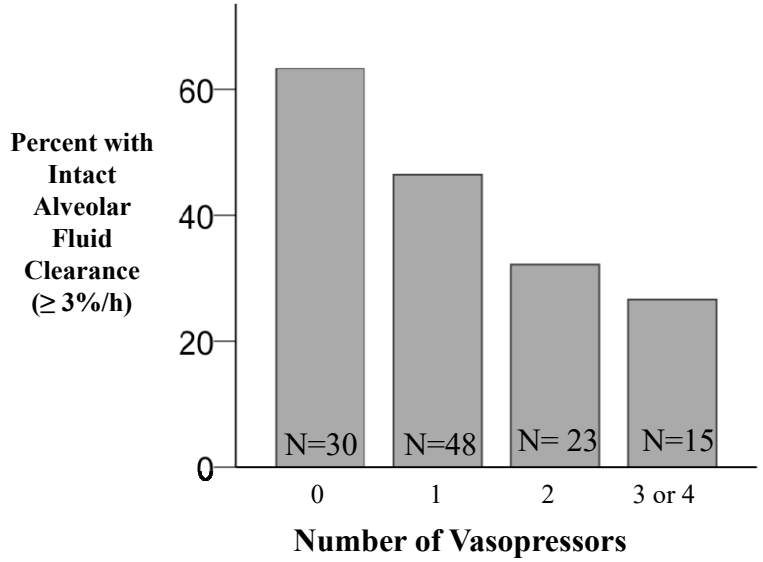
Impaired Alveolar Edema Fluid Clearance is Associated with Higher Mortality in Acute Lung Injury



Ware and Matthay, AJRCCM, 2001

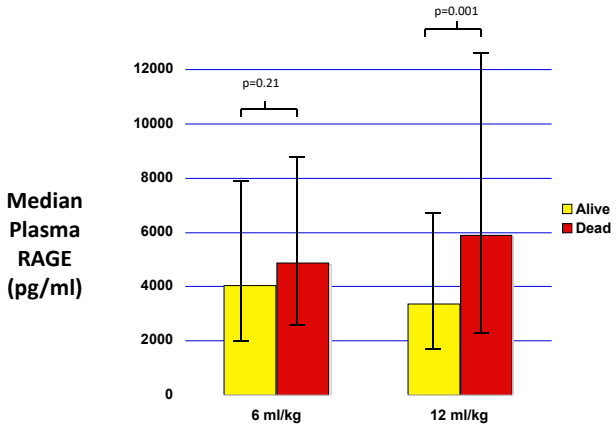
Ware and Matthay, Am J Resp Crit Care Med 2001

Alveolar Fluid Clearance Decreases Inversely with Number of Vasopressors in Patients with Sepsis



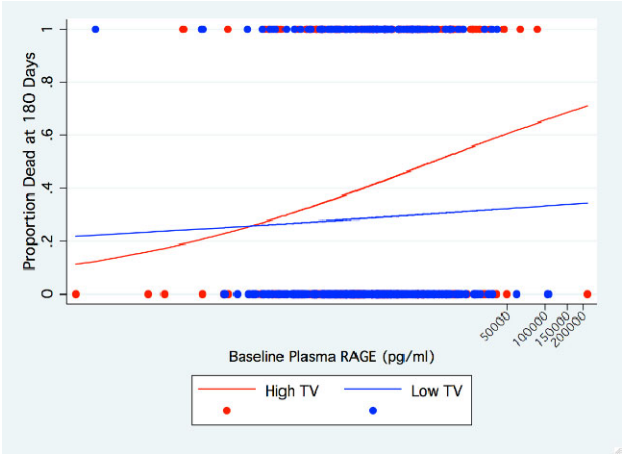
Zeyed JF et al, AJP:Lung, 2012

Elevated Baseline RAGE (Alveolar Epithelial Marker) Identified Patients with Higher Mortality



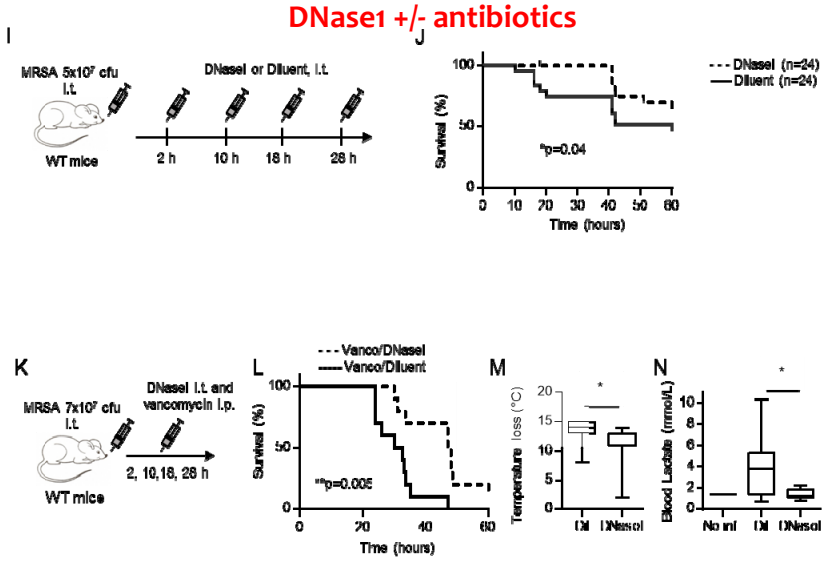
Calfee CS et al, *Thorax, 2008*

Patients with High Baseline Plasma RAGE levels had the Most Benefit from Low Tidal Volume – Illustrates Predictive Enrichment Concept



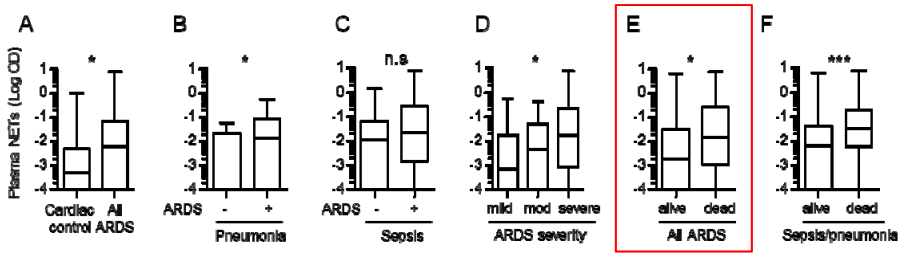
Calfee CS, Ware LB, Eisner MD, Parson PE, Thompson BT, Matthay MA, Thorax, 2008

Staph Aureus-Induced Acute Lung Injury in Mice – Role of Neutrophil Extracellular Traps (NETs) and Treatment with DNase1 +/- antibiotics



Lefrancais E, *et al. JCI Insight*, 2018

Translation to patients with ARDS: Elevated Plasma NETs in Patients Who Died with ARDS

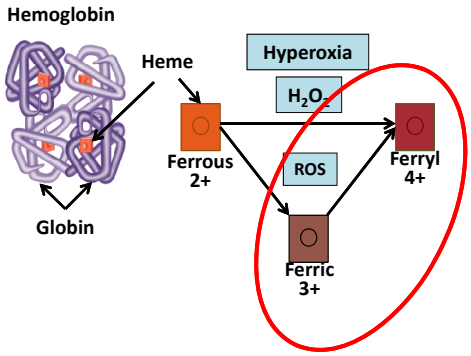


Higher Plasma NETs/DNase ratio in ARDS patients who died

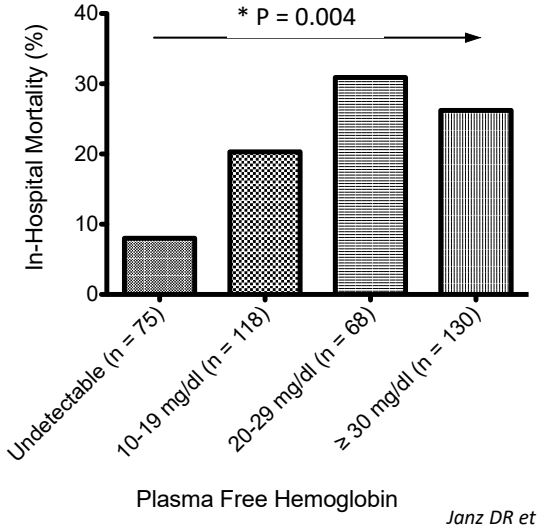
Lefrancais E, *et al. JCI Insight*, 2018.

Cell-Free Hemoglobin

- potent vasoconstrictor
- binds nitric oxide
- Ferryl (4^+) hemoglobin is a critical mediator of injury
- Mouse models and ex vivo perfused human lung show injurious effects in sepsis
- Acetaminophen blocks the injurious effects of cell-free hemoglobin in sepsis on acute kidney injury
- Example of point of care biomarker available now

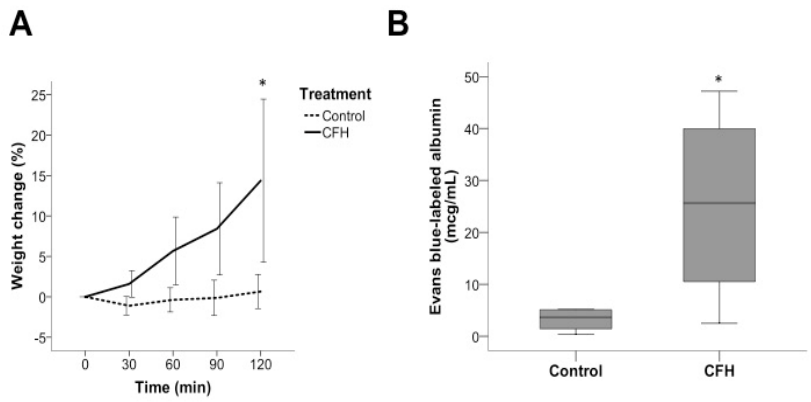


In 391 patients with severe sepsis, plasma levels of free hemoglobin are associated with hospital mortality



Janz DR et al, Crit Care Med 2013

Cell-free hemoglobin (CFH) in the perfusate increases vascular permeability in isolated perfused human lungs



N = 5 per group, * p = 0.047

N = 5 per group, * p = 0.027

Shaver et al, *JCI Insight*, 2018

What Have We Learned about Pathogenesis that Led to New Therapies for ARDS ?

- All based on improvements in supportive care
  - Low Tidal Volume (ARMA)
  - Fluid Conservative Therapy (FACTT)
  - Also neuromuscular blockade and prone positioning
- All stimulated by pre-clinical studies that suggested potential clinical benefit
  - Deleterious effects of high tidal volume *
  - Elevated intravascular hydrostatic pressure increased pulmonary edema in acute lung injury demonstrated in animal models**
  - Note the timeline from bench to bedside (20-25 years)

Webb & Tierney, 1974; Parker, 1984, Dreyfuss, 1991*

Staub, 1978; Prewitt, 1981; Sznajder, 1986; Schuster, 1987**

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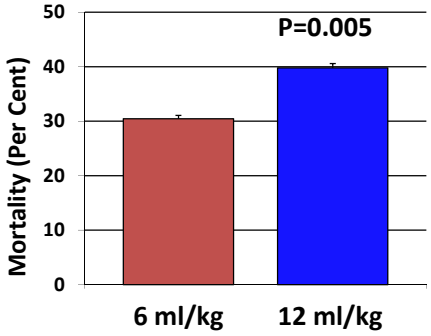
Biologic studies in plasma after randomization provided insights into the mechanisms of how low tidal volume reduced lung injury in the ARMA Trial



ARDS Network, NEJM, 2000

Reduced Plasma Levels in Lower Tidal Volume Group

- **Lower levels of IL-6**
- **Lower levels of IL-8**
- **Lower levels of TNR1**
- **Lower levels of SP-D**

Thorax, 2003
Crit Care Med, 2005
AJP:Lung, 2005

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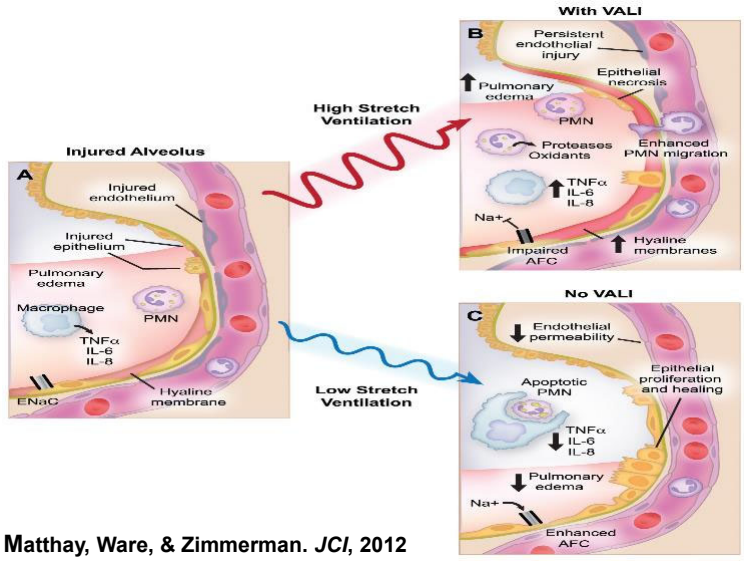
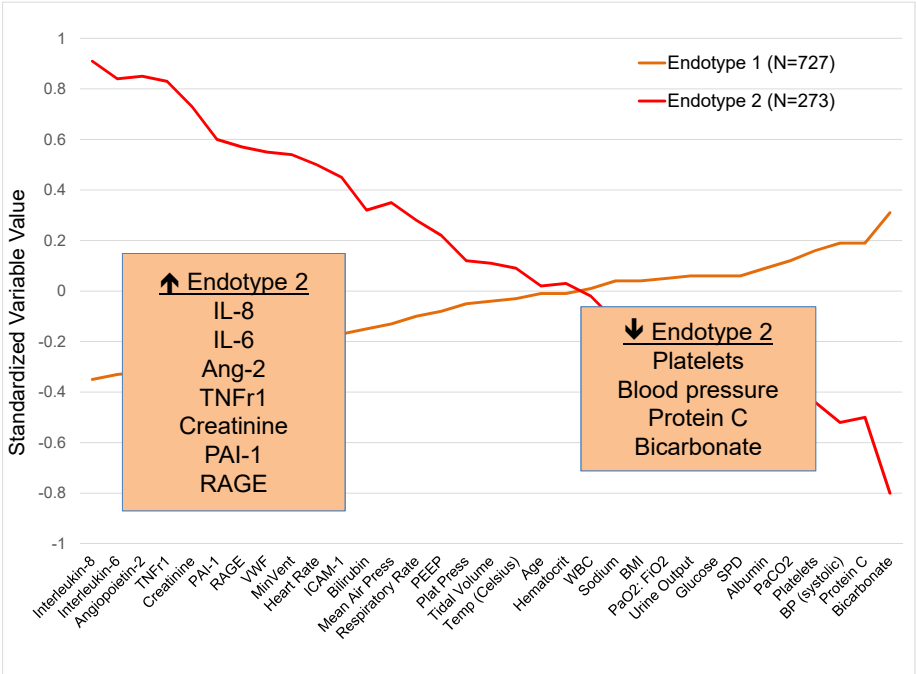
Lung Protective Ventilation Reduced Lung Endothelial and Epithelial Injury



Matthay, Ware, & Zimmerman. *JCI*, 2012

What Have We Learned about Heterogeneity from Secondary Analyses of ARDS Clinical Trials?

- Using latent class analysis for defining sub-groups of ARDS, Calfee and co-investigators have found a hyper and a hypo-inflammatory endotype in 5 clinical trials (ARMA, ALVEOLI, FACTT, SAILS, HARP-2)
- Emphasizes the potential value of using both biologic and clinical variables in defining ARDS for future interventions



Hyperinflammatory Endotype 2 Has Higher Mortality in FACTT Trial

	Endotype 1	Endotype 2	p-value
60-day mortality	21%	44%	<0.0001
90-day mortality	22%	45%	<0.0001
Ventilator-free days (mean)	15	8.8	<0.0001

Famous K et al, AJRCCM, 2017

A 3-Variable Model Accurately Identifies ARDS Endotype

	FACTT Derivation Cohort	ARMA Validation Cohort	ALVEOLI Validation Cohort
Top predictors from FACTT	AUC	AUC	AUC
3-variable model *(IL-8, bicarbonate, TNFr1)*	0.95	0.94	0.91
4-variable model *(IL-8, bicarbonate, TNFr1, vasopressor use)*	0.97	0.89	0.86
5-variable model *(IL-8, bicarbonate, TNFr1, vasopressor use, total minute ventilation)*	0.97	0.90	0.88

The NEW ENGLAND JOURNAL of MEDICINE

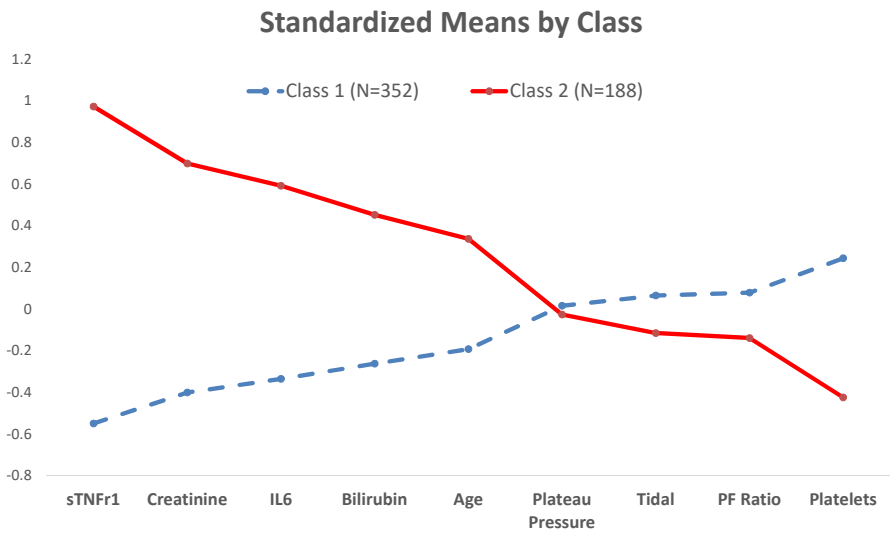
ORIGINAL ARTICLE

Simvastatin in the Acute Respiratory Distress Syndrome

Daniel F. McAuley, M.D., John G. Laffey, M.D., Cecilia M. O'Kane, Ph.D., Gavin D. Perkins, M.D., Brian Mullan, M.B., T. John Trinder, M.D., Paul Johnston, M.B., Philip A. Hopkins, Ph.D., Andrew J. Johnston, M.D., Cliona McDowell, M.Sc., Christine McNally, B.A., and the HARP-2 Investigators, for the Irish Critical Care Trials Group*

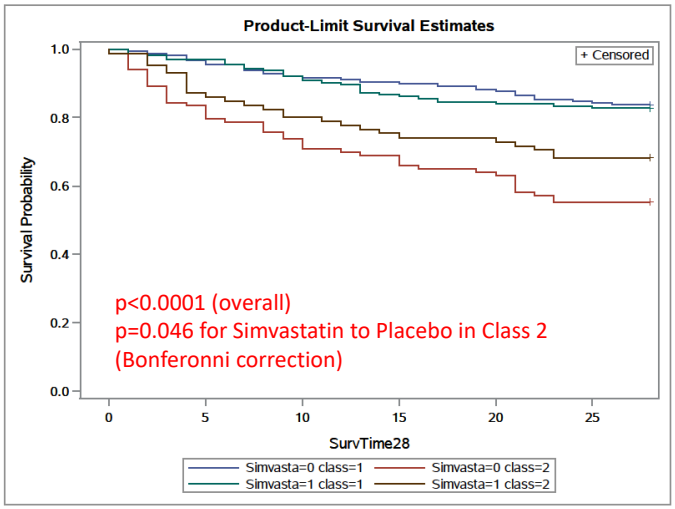
- Randomized controlled trial of simvastatin for ARDS conducted in UK/Ireland
- N=540
- Simvastatin 80 mg vs placebo
- Patients enrolled within 48 hrs of meeting ARDS criteria
- No difference in ventilator-free days, mortality

McAuley D et al, *NEJM* 2014



Calfee CS et al, Lancet Resp Med, 2018

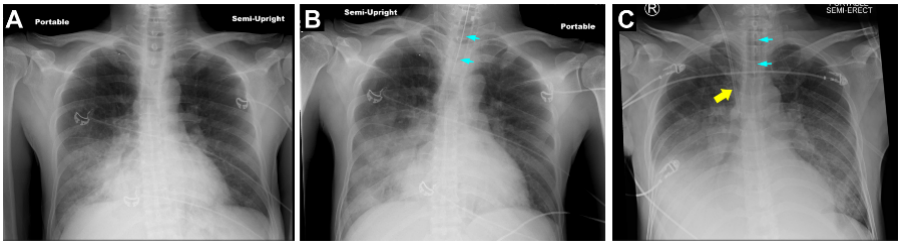
Survival Analysis to 28 Days – Simvistatin Reduced Mortality in the Class 2 Patients



Timing and Routes for Intervention for ARDS or Early Acute Lung Injury – 2019

- Early acute lung injury can be identified in the Emergency Department & the Intensive Care Unit
- Point of Care biological markers can help focus therapies on the higher risk patients
- Need to integrate biologic and clinical factors in clinical trial design, using both predictive and prognostic strategies
- Combination therapies may be needed, including beta agonists and steroids or cell-based therapies such as mesenchymal stromal cells

Pneumonia and Sepsis in the Emergency Department
Early Acute Lung Injury



Panel A – Lobar Bacterial Pneumonia
Panel B – Worsening Hypoxemia leading to Intubation
Panel C – Bilateral Infiltrates with ARDS plus CVP line for vasopressors

Matthay, et al. Lancet Resp Med, 2017

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Clinical Trials of Early Acute Lung Injury - Pneumonia and Sepsis in the Emergency Departmen

- Gong M et al, LIPS-A - JAMA, 2016 – ASA for prevention (LIPS-A clinical criteria) –limited value because less than 10% of patients identified who progressed to develop ARDS
- Festic … Levitt, Crit Care Med, 2018 – Inhaled steroids/beta agonists early treatment – successful phase 2a trial that reduced hypoxemia.
- NHLBI funded Prevention and Early Treatment of Acute Lung Injury (PETAL Network)(VIOLET – Vitamin D) and now CLOVERS – Fluid Liberal vs Fluid Conservative/Vasopressors)
- Frat JP et al, NEJM, 2015 – tested three modes of oxygen delivery in severe hypoxemic respiratory failure in spontaneously breathing patients in the ED - high flow nasal oxygen decreased mortality and decreased the intubation rate in patients with P/F < 200 mmHg. 48

What are the Next Steps to Optimize Treatments for ARDS?

- Need bedside point of care biologic assays in the ED and ICU to advance a personalized medicine strategy in critically ill patients with sepsis or early ARDS, such as plasma Hb and perhaps IL-8, Protein C, and bicarbonate
- Need to test prospectively these biologic measures in conjunction with the physiologic (RALE score, Dead Space, $Pa0_2/Fi0_2$ and PEEP), and clinical factors for classifying and stratifying patients (vasopressor shock for example)
- Test new treatments in the Emergency Department for early Acute Lung Injury (pneumonia and sepsis)
- Earlier recognition of ARDS and uniform implementation of low tidal volume are important

ADVANCES IN VENTILATOR MANAGEMENT OF ARDS

Angela Rogers, MD
Stanford University
Assistant Professor of Medicine

Friday, January 18, 2019 – 8:55 a.m. – 9:45 a.m.

Angela Rogers, MD, MPH, received her medical degree from Harvard Medical School, and her Masters in public health from the Harvard School of Public Health, and pursued post-graduate training at the Brigham and Women's Hospital and Harvard Combined fellowship. She is an Assistant Professor in Pulmonary and Critical Care Medicine at Stanford University, where her research focuses on using genetics and genomics to identify novel biology in ARDS.

Advances in Mechanical Ventilator Management in ARDS

Angela Rogers
Stanford University
California Thoracic Society
January 18, 2019

Conflict of Interest

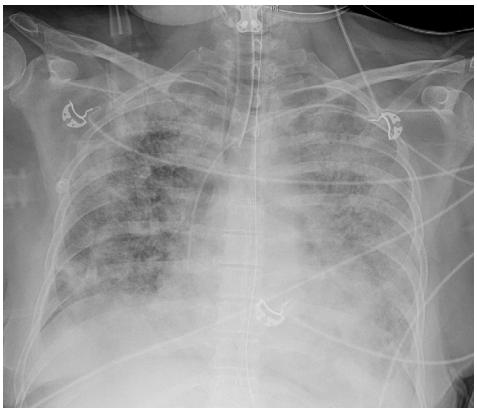
- I have no conflicts of interest

Learning Objectives

Mechanical Ventilation in ARDS:

- High flow oxygen therapy in early hypoxemic respiratory failure
- The critical importance of low tidal volume/low pressure ventilation
- PEEP in ARDS: Is there a role for personalized titration?
- New data for the role of ECMO in severe ARDS

A classic case of ARDS



- Intubated
- Acute
- P:F ratio <300
- Bilateral opacities
- Not explained by edema

Definition of ARDS

Acute Respiratory Distress Syndrome

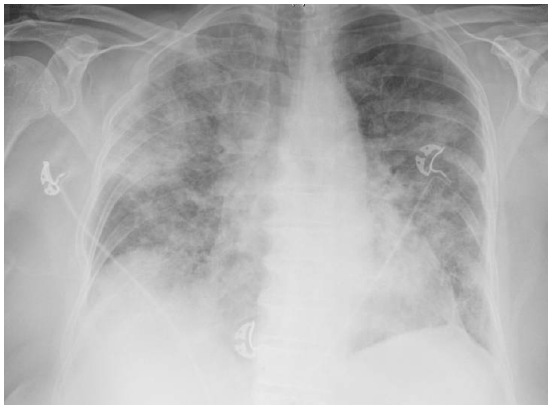
The Berlin Definition

The ARDS Definition Task Force*

- Bilateral infiltrates, acute (<7 days), not entirely explained by CHF, on 5 of PEEP
- Analyzed data from 7 ARDS datasets and >4400 patients
  - Severity classification:
    - Mild: PaO_2:FIO_2 200 - ≤300
    - Moderate: PaO_2:FIO_2 100 - ≤200
    - Severe: PaO_2:FIO_2 ≤100
  - Associated with mortality
    - 27%, 32%, and 45% with increasing severity

JAMA. 2012,307, 2526-2533

What if it's not quite ARDS?



What about this patient?:

- Not intubated!
- PO2 72 on 100% NRB
- Bilateral opacities

Hypoxic Respiratory Failure (HRF) definition in FLORALI High Flow O_2 Trial

High-Flow Oxygen through Nasal Cannula in Acute Hypoxemic Respiratory Failure

- Respiratory rate > 25
- PaO_2:FIO_2 < 300 on at least 10L/min flow x 15 min
- $PaCO_2$ <45
- No chronic respiratory failure

NEJM. 2015,372, 2185-2196

Treatment of Early HRF

High flow Oxygen (N 109)

Standard Oxygen (N 94)

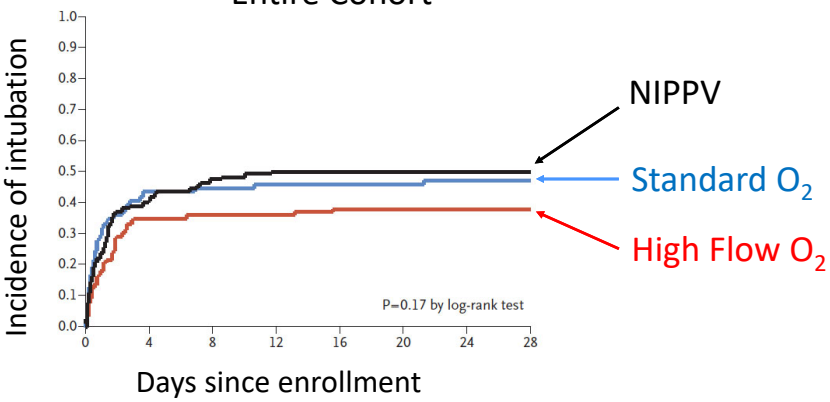
Noninvasive ventilation (N 110)

- Primary outcome: intubation rate
- Secondary outcomes:
  - ICU & 90-day mortality
  - Vent-free days by day 28

NEJM. 2015,372, 2185-2196

High flow for early HRF

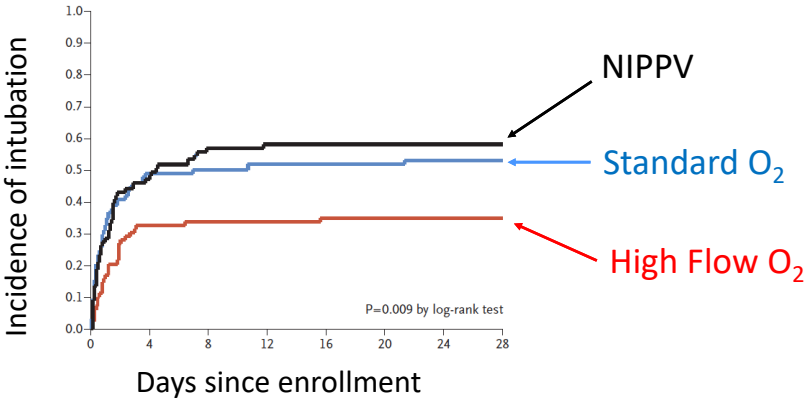
Entire Cohort



NEJM. 2015,372, 2185-2196

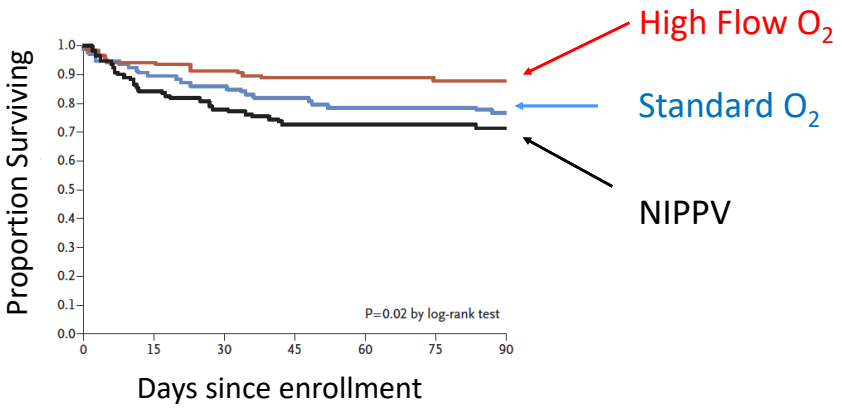
High flow for early HRF

Patients with P:F $\leq$ 200



NEJM. 2015,372, 2185-2196

High flow for early HRF

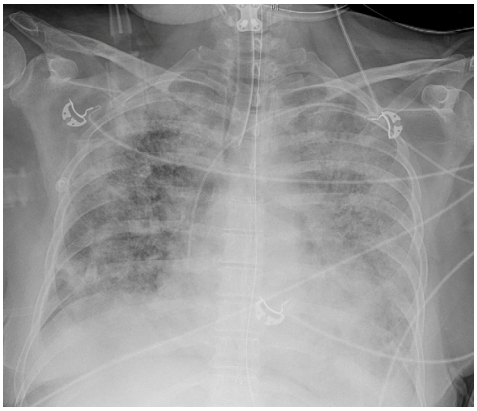


NEJM. 2015,372, 2185-2196

Take home #1:

- Prior to intubation in acute hypoxemic respiratory failure, consider high flow oxygen
  - Reduced mortality
  - Decreases need for intubation in sickest patients (PaO2:FIO2 $\leq$ 200).

What if it is ARDS?



What is the #1 thing we can do for this patient?

The #1 Way to treat ARDS: Low tidal volume ventilation

- Multicenter RCT
- 861 patients with ARDS (P:F $\leq$ 300)
- Randomized to 6-8 vs. 10-12 ml/kg TV
- Target plateau pressure < 30

	Low Tidal Volume	Traditional Tidal Volume	P-value
Death before discharge	31.0	39.8	.007
Ventilator free days	12	10	.007
Organ-failure free days	15	12	.006

NEJM. 2000,342, 1301-1308

What helps mortality in ARDS?

Definitive

Low tidal volume ventilation

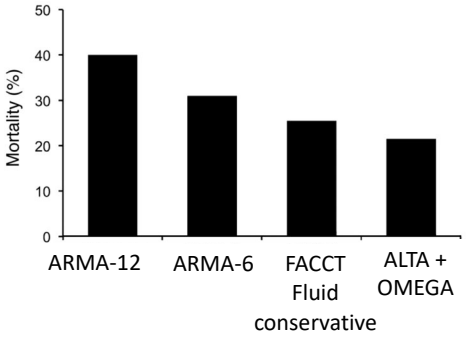
How good are we at implementing low tidal volume ventilation?: Lung Safe study in JAMA, 2016

- 459 ICUs from 50 countries across 5 continents x 1 month
- 29144 admitted
  - 10% fulfilled ARDS criteria
  - 23% of patients requiring mechanical ventilation

JAMA. 2016,315, 788-800

How good are we at implementing low tidal volume ventilation?: Lung Safe study in JAMA, 2016

- High mortality for ARDS in Lung Safe:
  - 34% mild
  - 40% moderate
  - 46% severe
- Ventilator strategy not ideal:
  - 1/3 of patients never recognized to have ARDS
  - P_{plat} measured in 40%
  - <2/3 receive TV ≤ 8 mg/kg
- Contrast with clinical trial mortality: 2000-2011



JAMA. 2016,315, 788-800
JCI 2012, 122(8):2731-2740

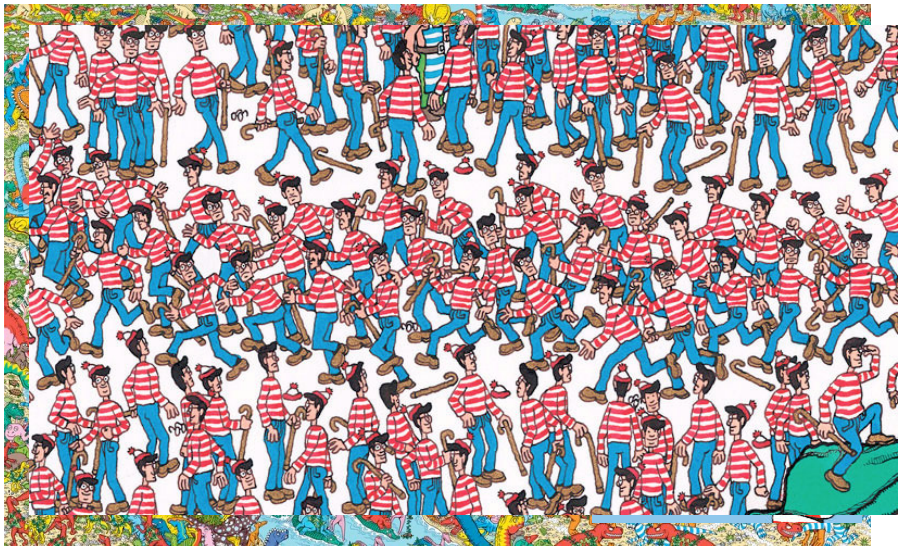
How good are we at implementing low tidal volume ventilation?: Lung Safe study in JAMA, 2016

Ventilator strategy in LUNG SAFE:

- 1/3 of patients never recognized to have ARDS
- P_{plat} measured in 40%
- Less than 2/3 received TV ≤ 8 mg/kg

JAMA. 2016,315, 788-800

ARDS is not unusual



Take home #2:

- ARDS is not unusual
- In real world practice:
  - mortality remains high
  - implementation of low tidal volume low pressure ventilator strategy is far from 100%

What helps beyond low tidal volume?

2 strategies for more severe ARDS (P:F<150)

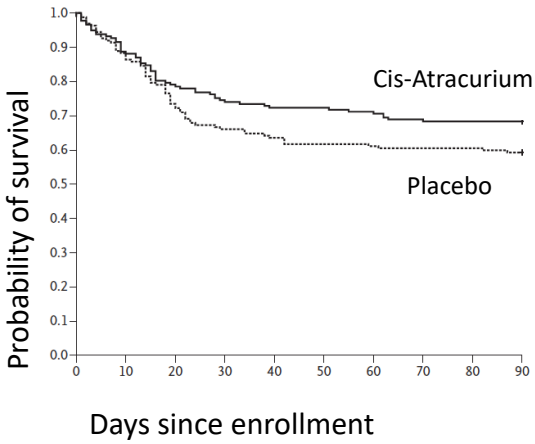
Neuromuscular blockade in ARDS

Neuromuscular Blockers in Early Acute Respiratory Distress Syndrome

- Multicenter RCT
- 340 patients with early, moderate-severe ARDS (P:F<150)
- Randomized to 48hr cis-atracurium vs placebo
- All received standard low tidal volume ventilation

NEJM. 2010, 373: 1107-16

Paralysis in severe ARDS



Lower hazard for death (.68, p=.04)

31.6% vs 40.7% 90-day mortality (p=.08)

NEJM. 2010, 373: 1107-16

Does treatment improve ARDS mortality?

Definitive	Probably*
Lung protective ventilation	Neuromuscular blockade (P:F<150)

* Probably = at least one multicenter RCT supports

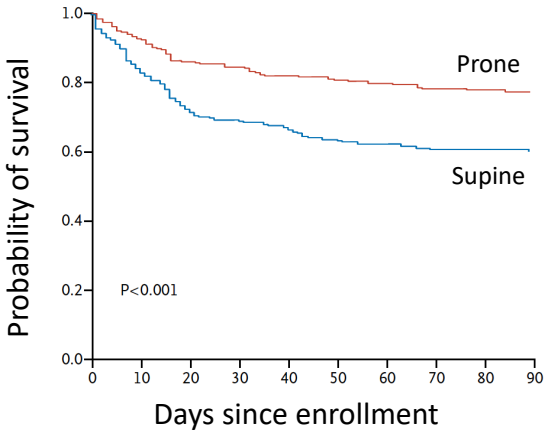
Prone positioning in severe ARDS

Prone Positioning in Severe Acute Respiratory Distress Syndrome

- Multicenter RCT
- 466 patients with early, moderate-severe ARDS (P:F<150)
- Randomized to 16h/day prone positioning vs standard low tidal volume ventilation

NEJM. 2013, 368: 2159-67

Prone positioning in severe ARDS



16% vs 32.8% 28d mortality (p<.001)

23.6 vs 41% 90d mortality (p<.001)

NEJM. 2013, 368: 2159-67

Does treatment improve ARDS mortality?

Definitive	Probably*
Lung protective ventilation	Neuromuscular blockade (P:F<150)
	Prone positioning (P:F<150)

* Probably = at least one multicenter RCT supports

Take home #3

- In *early*, moderate to severe ARDS, consider paralytic and proning.
- Especially watch for ventilator dyssynchrony

What about PEEP in ARDS?

ALVEOLI study

- 549 patients with ARDS (P:F<300)
- Randomized to high or low PEEP

	Low PEEP	High PEEP	P-value
Death before discharge	25	28	.48
Ventilator free days	14.5	13.8	.5
Organ-failure free days	16	16	.8

NEJM. 2004,351: 327-336

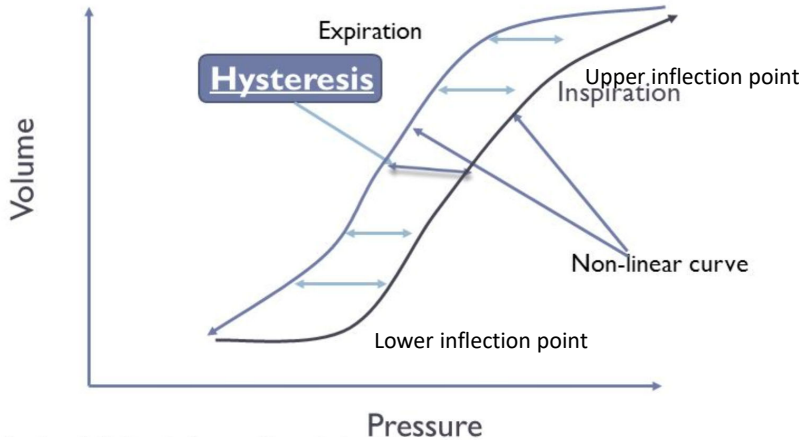
Maybe high PEEP helps some in ARDS

- Meta-analysis of 2299 patients in 3 ARDS trials of low vs. high PEEP
- No difference in mortality in all patients
- But! PEEP effects differ with ARDS severity

P:F Ratio	60 day hazard: death with high PEEP	P value
<200	.85	.03
200-300	1.32	.2

JAMA. 2010, 303: 865-873

PEEP in ARDS: Does 1 size fit all?



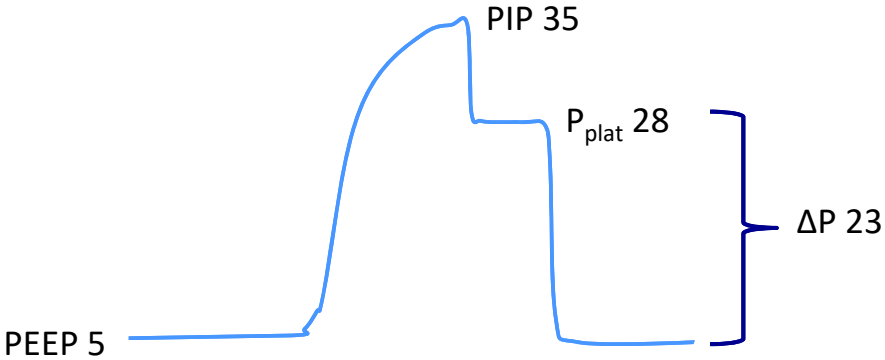
PEEP in ARDS: Does 1 size fit all?

Driving Pressure and Survival in the Acute Respiratory Distress Syndrome

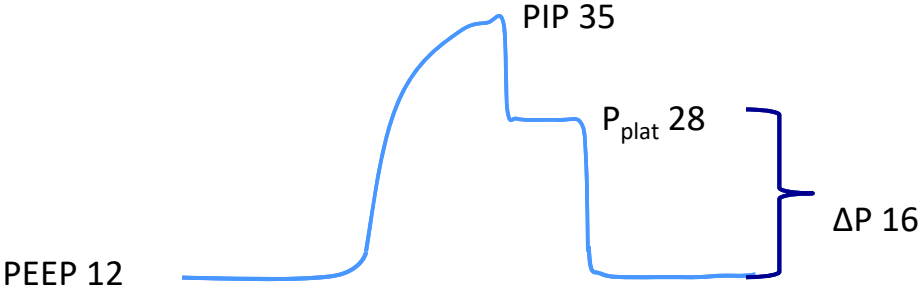
- 3562 patients in 9 RCTs of ARDS
- Is it volume or pressure that matters?
- Examined the driving pressure (ΔP)
  - $\Delta P = V_T/C_{RS}$
  - If no inspiratory effort $\Delta P = P_{plat}$-PEEP

NEJM. 2015, 372: 747-755

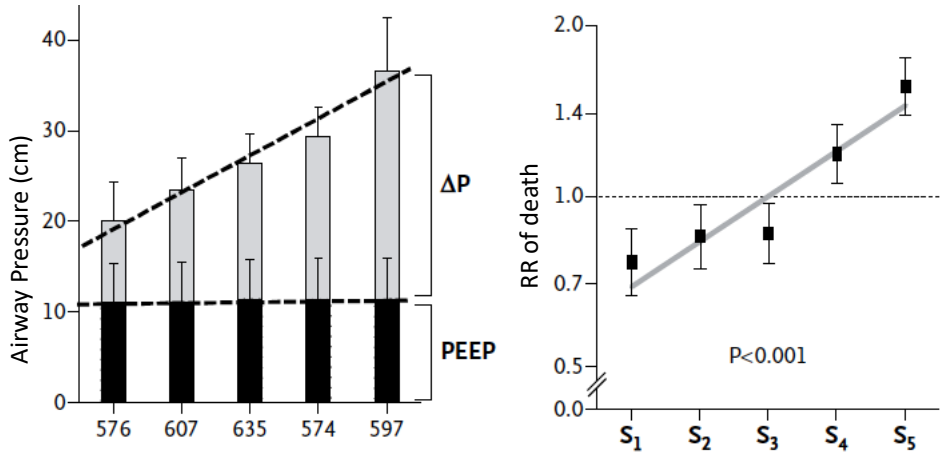
PEEP in ARDS: Does 1 size fit all?



PEEP in ARDS: Does 1 size fit all?

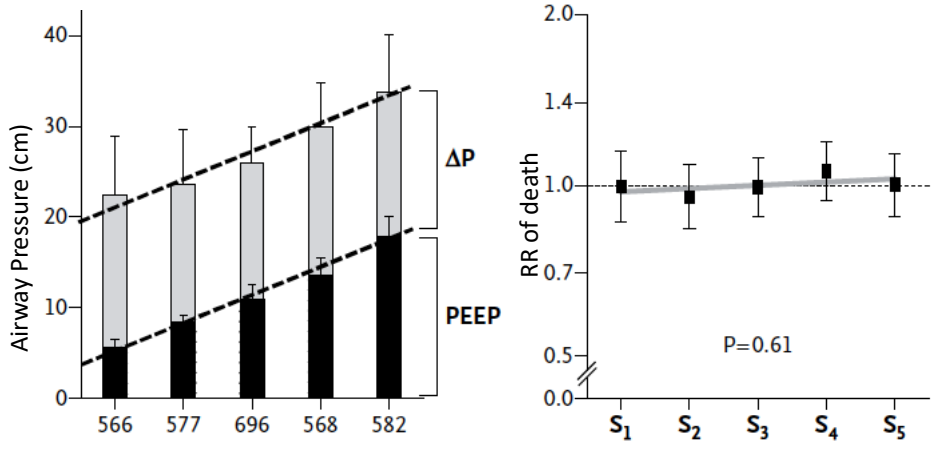


PEEP in ARDS: Does 1 size fit all?
Constant PEEP, changing P_{plat}



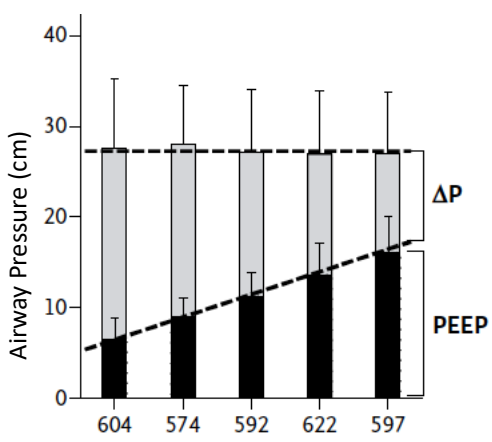
NEJM. 2015, 372: 747-755

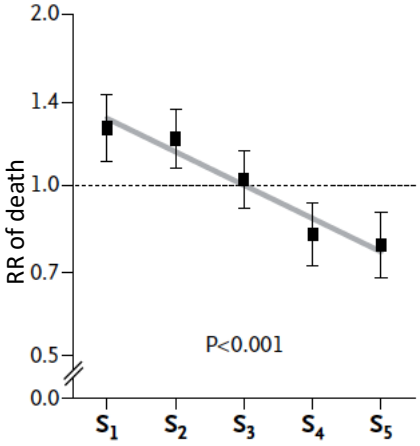
PEEP in ARDS: Does 1 size fit all?
Constant delta P, rising pPlat



NEJM. 2015, 372: 747-755

PEEP in ARDS: Does 1 size fit all?
Constant Pplat, rising PEEP/falling Delta P

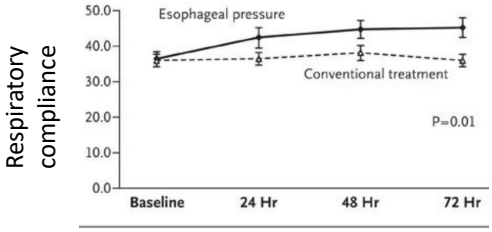


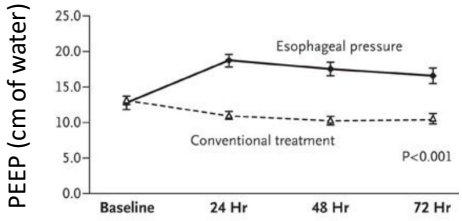


NEJM. 2015, 372: 747-755

PEEP in ARDS: Titration by esophageal balloon

- Single center RCT
- 61 patients
- PaO_2:FIO_2<300
- Control arm: standard ARDS ventilation
- Trend toward lower mortality
  - ~39 vs 17% p = .06





NEJM. 2008, 359: 2095-2104

Does treatment improve ARDS mortality?

Definitive	Probably*	No (partial list)
Lung protective ventilation	Neuromuscular blockade (P:F<150)	
	Prone positioning (P:F<150)	
	High or tailored PEEP	But! Tailored PEEP had not been tested in an RCT

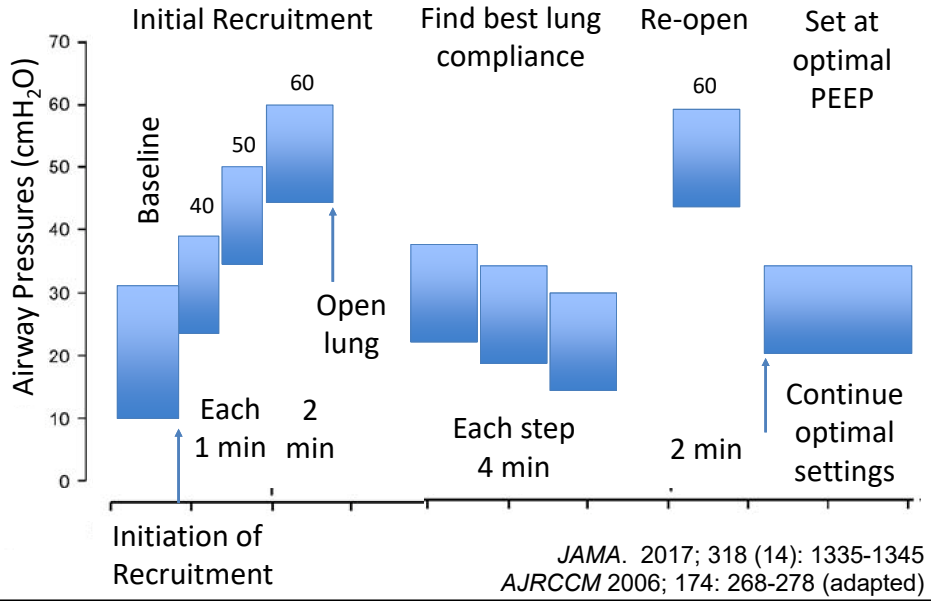
* Probably = at least one multicenter RCT supports

A trial of Titrated PEEP in ARDS
the ART study, JAMA 2017

- 1010 pts in 9 countries
- Randomized to standard ARDSNet PEEP vs tailored PEEP
- P:F<200
- 65% had shock

JAMA. 2017; 318 (14): 1335-1345

Trial design: recruitment maneuver

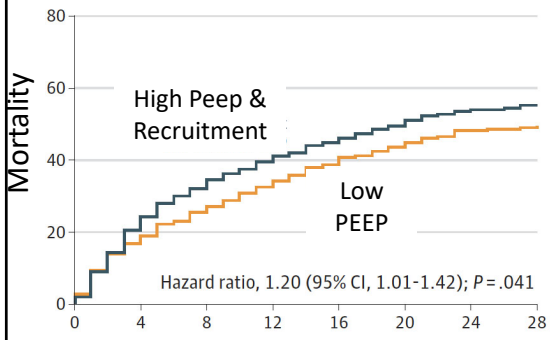


JAMA. 2017; 318 (14): 1335-1345
AJRCCM 2006; 174: 268-278 (adapted)

Trial design: recruitment maneuver

- After 500 pts and 3 cardiac arrests
  - 25 x 1 min, 30 x 1 min, 35 x 1 min
  - Start at 23 and go down q 3 min
  - Re-recruit at 35

High/tailored PEEP didn't help



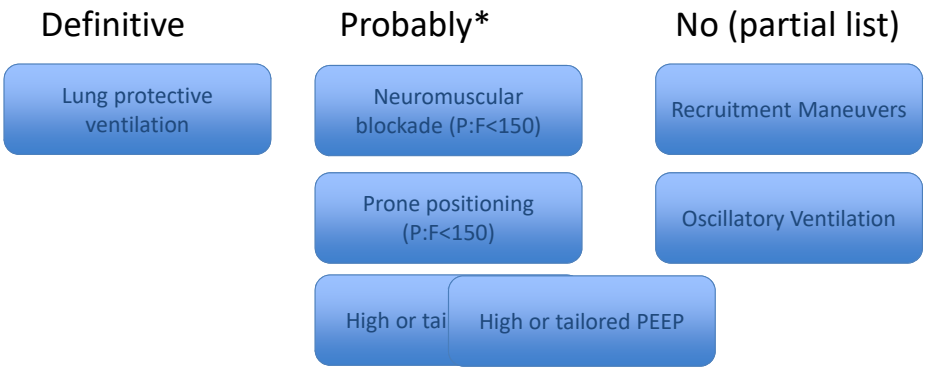
	Titrated PEEP	Traditional PEEP
28d mortality	55%	49%
PEEP	16	12
Driving Pressure	11.7	13.5

JAMA. 2017; 318 (14): 1335-1345

Take home #4 on PEEP:

- Increasing evidence shows that, especially for more severe ARDS, higher PEEP likely helps
- Targeting PEEP to the patient (by doing ΔP titration or esophageal balloon) is intriguing but not yet proven in RCT
- Avoid prolonged, high pressure recruitment manouvers

Does treatment improve ARDS mortality?



* Probably = at least one multicenter RCT supports

ECMO for the sickest of the sick

- ECMO for severe ARDS: EOLIA trial
- Is ECMO better for severe ARDS?
  - Very severe ARDS, intubated <7 days with:
    - P:F<50 for 3h
    - P:F<80 for 6h
    - pH<7.25 with PCO2 >60 for 6h
  - Above values on 6 ml/kg, PEEP >=10, Pplat<32

NEJM. 2018, 378: 1965-75

ECMO (EOLIA trial)

- Key points:
  - Great adherence to standard of care (90% proned, all paralyzed, 83% inhaled NO or flolan, all low tidal volume prior to enrollment)
  - Strict crossover rule!!
    - O2 sat <80% for >6h
    - No irreversible organ damage/chance for survival
  - Powered for large absolute risk difference (60% to 40% mortality)

NEJM. 2018, 378: 1965-75

ECMO: EOLIA

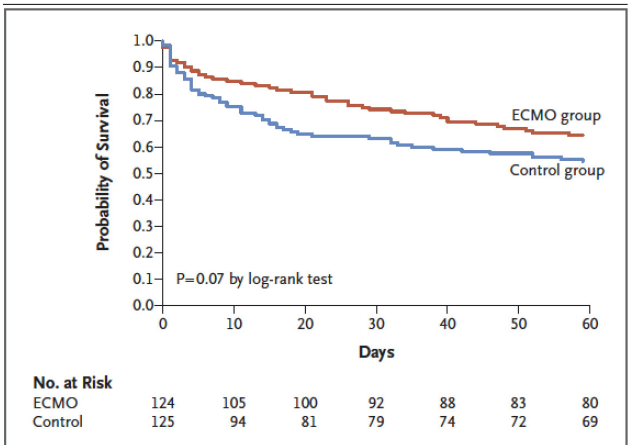


Figure 2. Kaplan–Meier Survival Estimates in the Intention-to-Treat Population during the First 60 Days of the Trial.

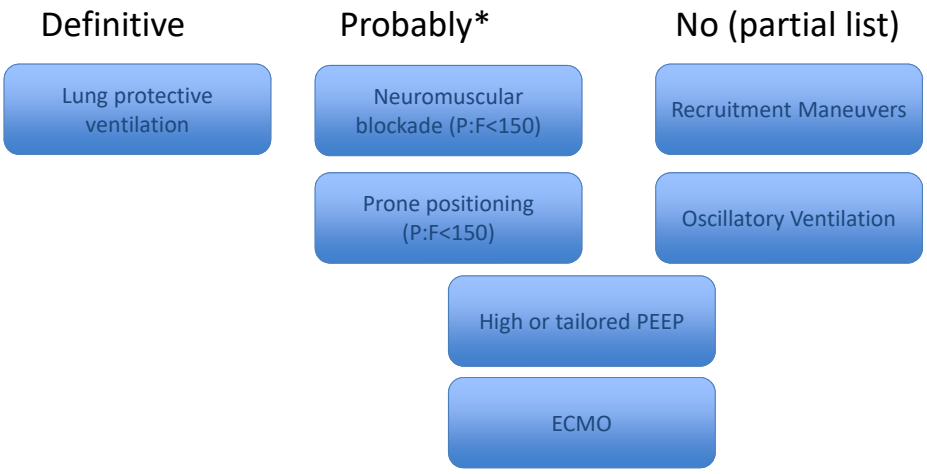
Stopped for futility, 249 pts in 6y

35% vs 46% 60d mortality (p= .09)

35 ctrl pts (28%) crossed over to ECMO, 9 after cardiac arrest, 11 on CRRT, 57% mort

NEJM 2018

Does treatment improve ARDS mortality?



* Probably = at least one multicenter RCT supports

Take home points recapped!

- In early respiratory failure consider high flow
- Low tidal volume, low pressure ventilation is still the #1 maneuver for ARDS mechanical ventilation
  - A LOT of patients meet ARDS criteria
  - We miss it often
- If mod-severe ARDS: paralytic and proning early
- PEEP: Higher probably better, especially in moderate to severe ARDS
  - consider titration to best compliance
- Consider ECMO in the sickest patients

BREAK
EXHIBIT HALL OPEN

Friday, January 18, 2019 – 9:45 a.m. – 10:00 a.m.

DRIVING PRESSURE AND LUNG MECHANICS

Atul Malhotra, MD
UC San Diego
Professor of Medicine and Sleep Specialist

Friday, January 18, 2019 – 10:00 a.m. – 10:45 a.m.

Atul Malhotra, MD, is a board-certified pulmonologist, intensivist and chief of Pulmonary, Critical Care and Sleep Medicine. He is active clinically in pulmonary, critical care and sleep medicine. In the sleep clinic, he provides a full spectrum of diagnostic and therapeutic services to patients with sleep-related disorders, including sleep apnea, insomnia, restless leg syndrome, narcolepsy and sleep disorders associated with medical or psychiatric conditions. He has a special interest in the treatment of sleep apnea.

Dr. Malhotra is the president of the American Thoracic Society. He has taught and presented his research on sleep-related disorders locally, regionally, nationally and internationally. He has published more than 200 original manuscripts in leading journals. He is a principal- and co-investigator on numerous projects relating to sleep apnea and serves as an ad hoc reviewer for many leading journals including the New England Journal of Medicine, Mayo Clinic Proceedings, Sleep and the Journal of American Medical Association. To view a full list of his publications, visit PubMed.

As a professor in the Department of Medicine, Dr. Malhotra is involved in training medical students, residents and fellows at UC San Diego School of Medicine.

Before joining UC San Diego Health, Dr. Malhotra practiced pulmonary, critical care and sleep medicine at Massachusetts General Hospital, Beth Israel Deaconess Medical Center and Brigham and Women's Hospital. He also served as attending physician in intensive care at King Faisal Hospital in Rwanda. He was associate professor at Harvard Medical School and medical director of the Brigham and Women's Hospital Sleep Disorders Research Program.

Dr. Malhotra completed his fellowship training in pulmonary and critical care medicine at Harvard Medical School and a residency in internal medicine at the Mayo Clinic. He completed an internship at St. Thomas Medical Center in Akron, OH and received his medical degree from the University of Alberta in Canada. Dr. Malhotra is triple board-certified in pulmonary disease, sleep medicine and critical care medicine.

Acute Respiratory Distress Syndrome
Lung Mechanics and Driving Pressure

Atul Malhotra, MD

Pulmonary, Critical Care and Sleep Medicine
UC San Diego

Obesity and the lung: 3 · Obesity, respiration and intensive care

A Malhotra,[1] D Hillman[2]

Outline

- 1. Obesity effects on the abdomen
- 2. Obesity effects on the respiratory system
- 3. Implications for mechanical ventilation

Thorax 2008

Abdominal Compartment Syndrome

- **Syndrome well recognized by surgeons**
- **Increasing evidence in Medical ICU patients**
- **Transduce Foley catheter or paracentesis needle or measure gastric pressure**

Intensive Care Med (2004) 30:822–829
DOI 10.1007/s00134-004-2169-9

ORIGINAL

Manu L. N. G. Malbrain
Davide Chiumello
Paolo Pelosi
Alexander Wilmer
Nicola Brienza
Vincenzo Malcangi

Prevalence of intra-abdominal hypertension in critically ill patients: a multicentre epidemiological study

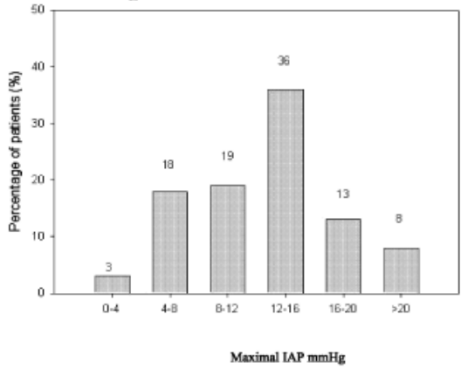
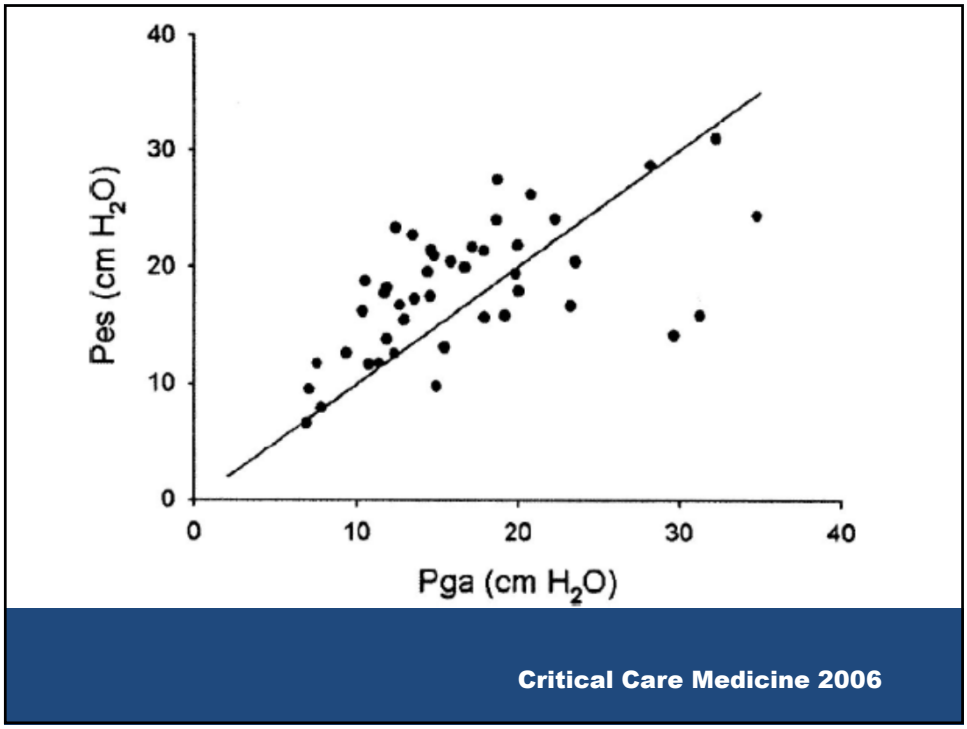
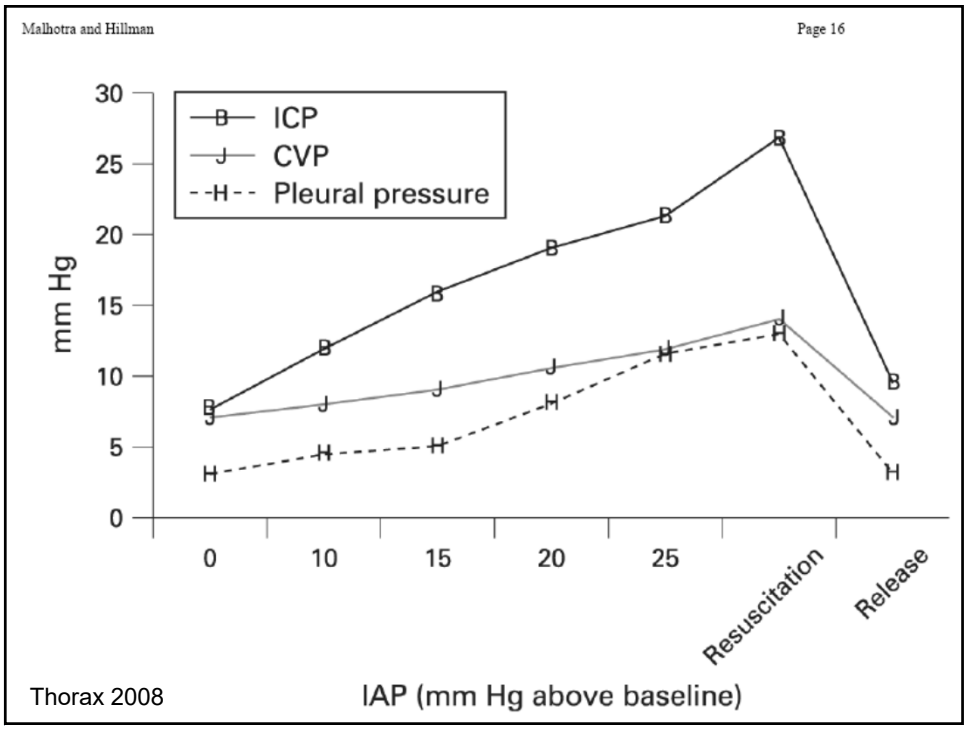


Fig. 1 Gaussian distribution of maximal intra-abdominal pressure (*IAP*) during the study day

- **50% had IAP > 12 mmHg**
- **8% had ACS**
- **BMI was the only significant independent predictor of IAP in multivariate analysis**



Critical Care Medicine 2006



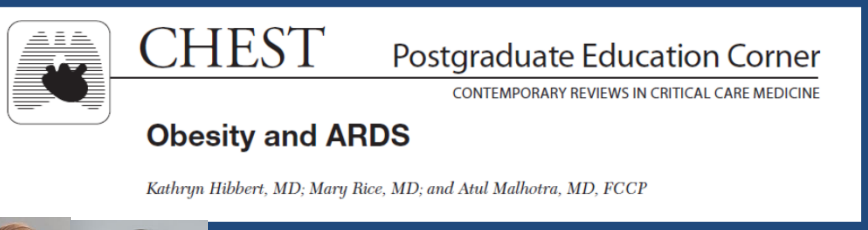
Thorax 2008

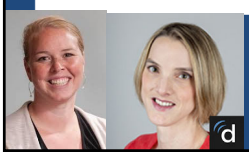
Summarize ACS

- **Elevated IAP is common in obesity**
- **Important effects on abdominal viscera**
- **Raised pleural pressure has implications for mechanical ventilation**
- **Awareness of pleural pressure is critical for interpretation of CVP and Wedge**
- **Raised ICP may respond to laparotomy**

Outline

- 1. Obesity effects on the abdomen
- 2. Obesity effects on the chest wall/lung
- 3. Implications for mechanical ventilation


CHEST Postgraduate Education Corner
CONTEMPORARY REVIEWS IN CRITICAL CARE MEDICINE
Obesity and ARDS
Kathryn Hibbert, MD; Mary Rice, MD; and Atul Malhotra, MD, FCCP

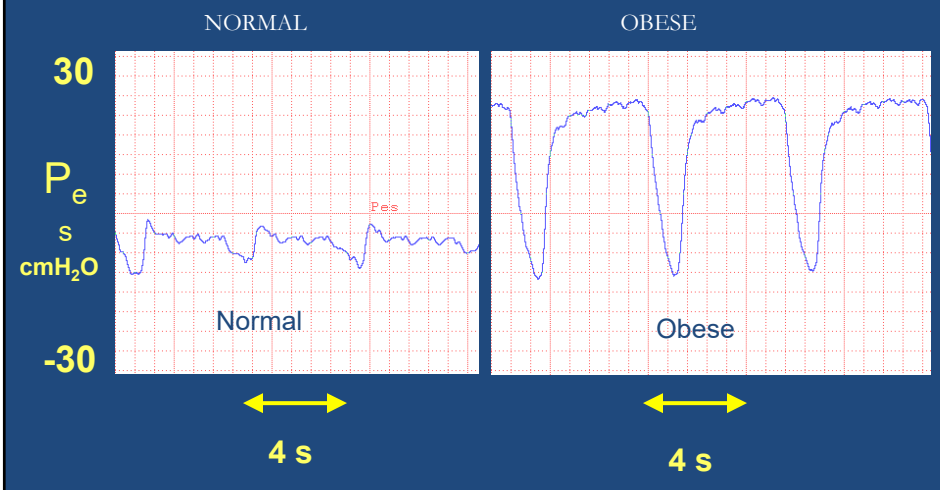


Thorax 2008; Chest 2012

Obesity Effects on Chest Wall

- **Compliance of the lung but not the chest wall is reduced in a number of obesity studies.**
- **Baseline position is altered i.e. pleural pressure is positive but pressure/volume characteristic is preserved.**

Pes in normal and obese subjects at rest, lateral recumbent.



Owens et al. Obesity 2012

Compliance of the respiratory system and its components in health and obesity[1]

A. NAIMARK[2] AND R. M. CHERNIACK[3]
Faculty of Medicine, University of Manitoba; and Clinical Investigation Unit, Department of Medicine, Winnipeg General Hospital, Winnipeg, Canada

- **Studied modest obesity by today's standards**
- **Normal lung compliance**
- **Reduced chest wall compliance**
- **Likely confounded by behavioral influences during wakefulness i.e chest wall muscle activity**

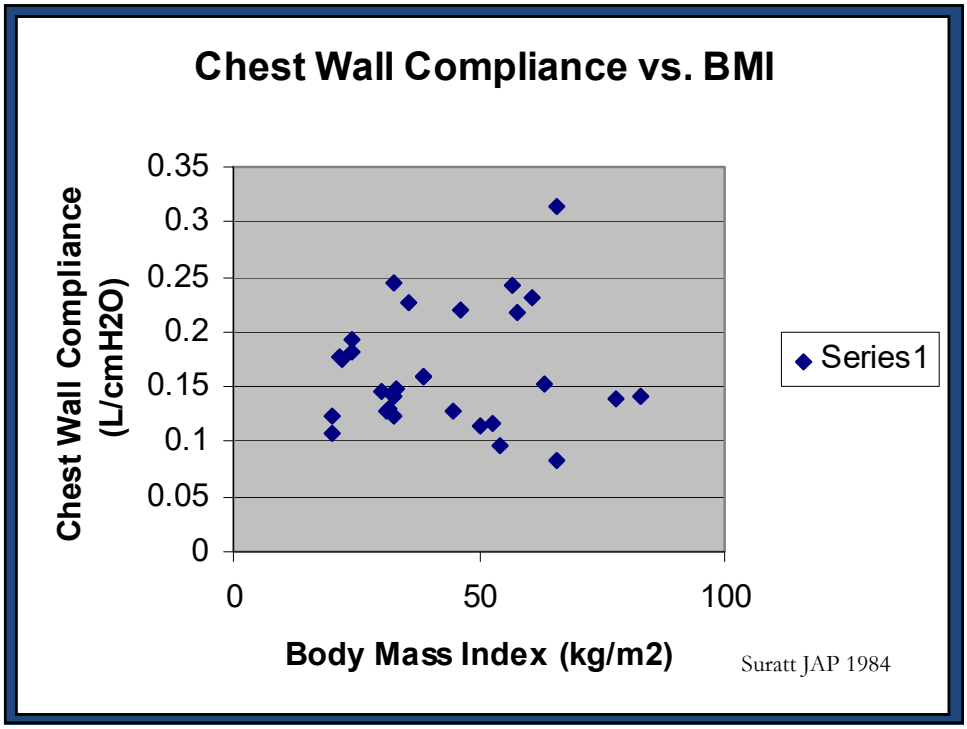
JAP 1960 Cherniack

Compliance of chest wall in obese subjects

PAUL M. SURATT, STEPHEN C. WILHOIT, HENRY S. HSIAO, RICHARD L. ATKINSON, AND DUDLEY F. ROCHESTER
Department of Internal Medicine, University of Virginia School of Medicine and Pulmonary Function Laboratory, University of Virginia Hospital, Charlottesville, Virginia 22908, and Department of Surgery, University of North Carolina, Chapel Hill, North Carolina 27514

- **Early chest wall studies were likely confounded by behavioral influences**
  - **e.g. muscle activity during wakefulness**
- **Subsequent studies done during relaxed wakefulness or paralysis or sleep**
- **Chest wall compliance is likely normal in obesity**

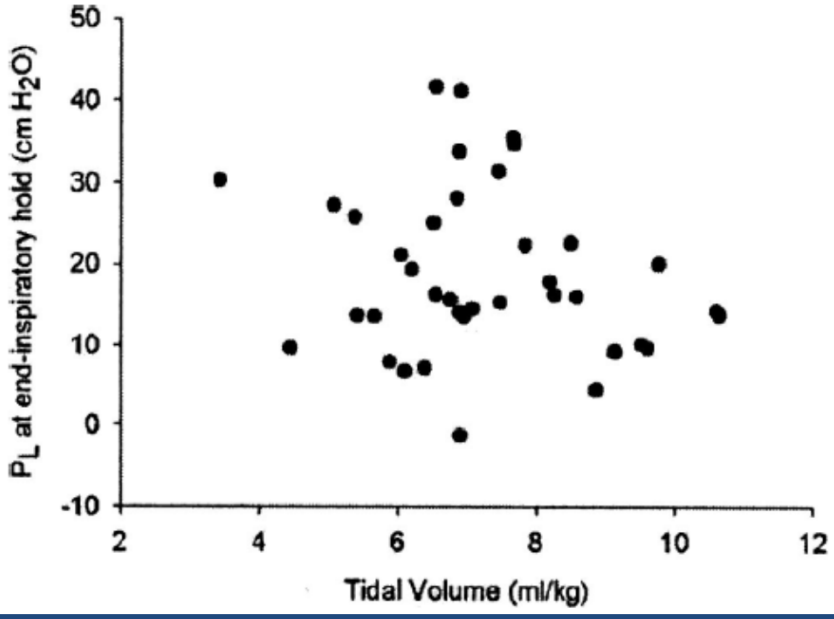
JAP 1984



Esophageal and transpulmonary pressures in acute respiratory failure*

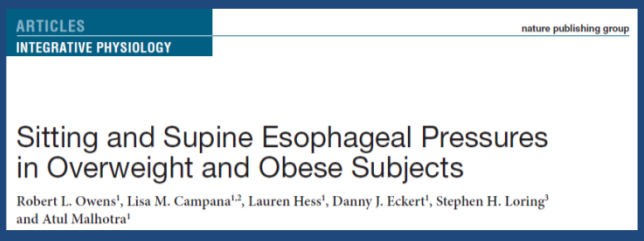
Daniel Talmor, MD, MPH; Todd Sarge, MD; Carl R. O'Donnell, ScD; Ray Ritz, RRT; Atul Malhotra, MD; Alan Lisbon, MD; Stephen H. Loring, MD

CCM 2006



Summarize Obesity and Chest Wall

- Most data indicate that the lung not the chest wall is stiff
- Evidence of alveolar collapse suggests benefits to PEEP
- Airway opening pressures tell us little about distending pressures across the lung.
- 6 cc/kg tidal volume gives variable lung stretch.


ARTICLES
INTEGRATIVE PHYSIOLOGY
nature publishing group

Sitting and Supine Esophageal Pressures in Overweight and Obese Subjects

Robert L. Owens[1], Lisa M. Campana[1,2], Lauren Hess[1], Danny J. Eckert[1], Stephen H. Loring[3] and Atul Malhotra[1]

Obesity 2012

Outline

- 1. Obesity effects on the abdomen
- 2. Obesity effects on the chest wall/lung
- 3. Implications for mechanical ventilation

Thorax 2008

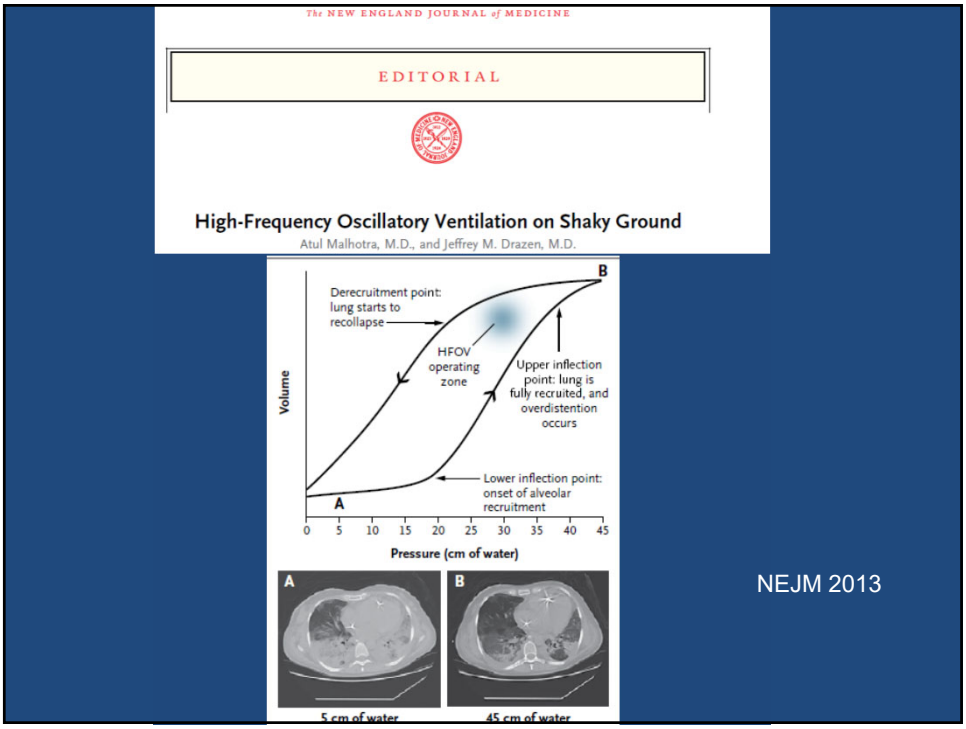
How Many Have a Good Sense How to Ventilate this patient ?

- 45 year old with bilateral infiltrates has ABG of pH=7.35 PaCO2=43 mmHg, PaO2=70 mmHg on FIO2=0.6
- Who would give PEEP=8 cmH2O vs. 15 cmH2O?

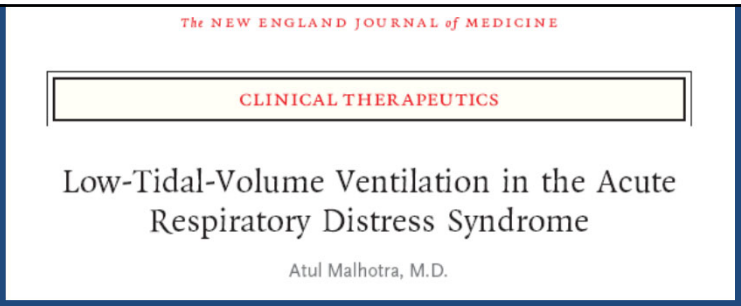
Malhotra et al, NEJM CPC 2003

Table 4. Effects of Positive End-Expiratory Pressure in Patients with Congestive Heart Failure.

Reduced preload due to increased vena caval resistance
Reduced left ventricular afterload due to reduced wall stress
Reduced myocardial oxygen consumption due to decreased ventricular size
Increased lung compliance due to reduced extravascular lung fluid
Decreased negative pleural pressure with inspiration
Suppressed catecholamines due to improved cardiac output and oxygenation
Reduced mitral regurgitation



NEJM 2013


The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL THERAPEUTICS

Low-Tidal-Volume Ventilation in the Acute Respiratory Distress Syndrome

Atul Malhotra, M.D.

Conservative views expressed

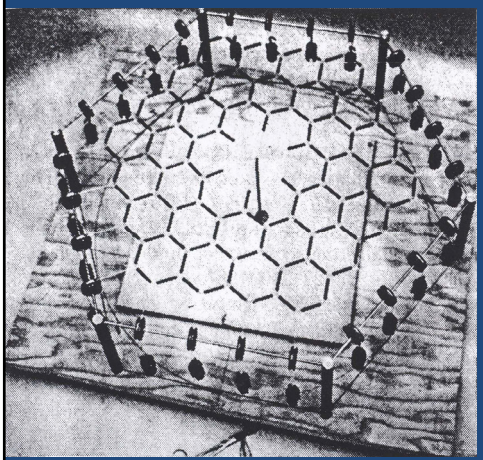
6 cc/kg volume pre-set is the gold standard

Lower is better

Goal is to do no harm with ventilator i.e. prevent mechanical injury

NEJM 9/07

Stress Concentration



- Estimated concentration of stress could be > 4 times that applied to the airway
- Airway pressure of 30 cmH_2O ≈ 140 cm H_2O in some regions

Mead, *JAP* 1970, 28(5):596

JOURNAL OF APPLIED PHYSIOLOGY
Vol. 28, No. 5, May 1970. *Printed in U.S.A.*

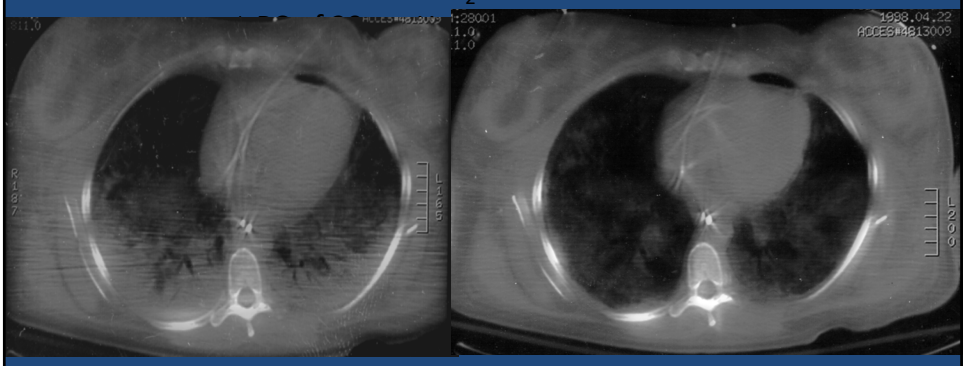
Stress distribution in lungs: a model of pulmonary elasticity

JERE MEAD, TAMOTSU TAKISHIMA, AND DAVID LEITH
Department of Physiology, Harvard University School of Public Health, Boston, Massachusetts 02115

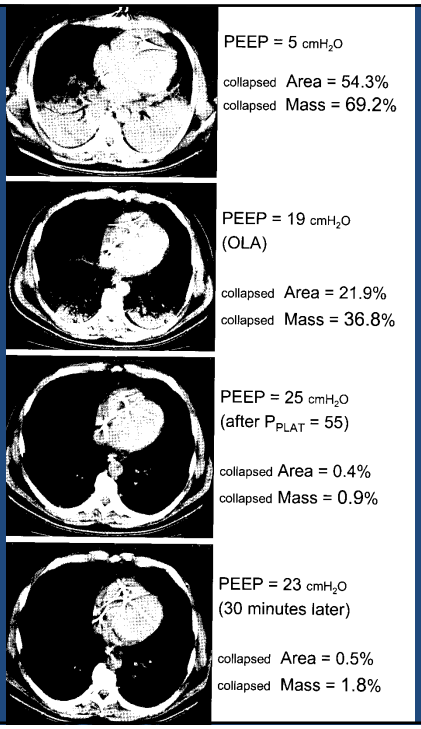
- **Very high shear forces can occur at junctions of normal and abnormal lung**
- **No safe pressure (AJRCCM 2007)**
- **Strategies to promote homogeneity may promote lung protection**
- **"get it open, leave it open"**
- **Homogeneity is everything**

Cytokine Release Following Recruitment Maneuvers*

Daniel Talmor, MD, MPH, FCCP; Todd Sarge, MD; Anna Legedza, ScD; Carl R. O'Donnell, ScD; Ray Ritz, RRT; Stephen H. Loring, MD; and Atul Malhotra, MD, FCCP



Crit Care Med 2000, Chest 2007



Baptista et al AJRCCM 2006

EFFECT OF A PROTECTIVE-VENTILATION STRATEGY ON MORTALITY IN THE ACUTE RESPIRATORY DISTRESS SYNDROME

MARCELO BRITTO PASSOS AMATO, M.D., CARMEN SILVIA VALENTE BARBAS, M.D., DENISE MACHADO MEDEIROS, M.D., RICARDO BORGES MAGALDI, M.D., GUILHERME DE PAULA PINTO SCHETTINO, M.D., GERALDO LORENZI-FILHO, M.D., RONALDO ADIB KAIRALLA, M.D., DANIEL DEHEINZELIN, M.D., CARLOS MUNOZ, M.D., ROSELAINE OLIVEIRA, M.D., TERESA YAE TAKAGAKI, M.D., AND CARLOS ROBERTO RIBEIRO CARVALHO, M.D.

- **Open Lung Ventilation**
- **PEEP > Pflex and Plateau < UIP**
- **Permissive hypercapnia and recruitment maneuvers**
- **Studied n=53 RCT sick patients**
- **28 day survival 71% vs 38%**

Amato et al NEJM 1998; Ranieri JAMA 1999

Amato – caveats?

- **Some have argued 71% control mortality too high (3.6 organ failures)**
- **Small sample size???**
- **Findings confirmed by Ranieri et al. who demonstrated lower cytokines using lung protective strategy**

Ranieri JAMA 1999

A high positive end-expiratory pressure, low tidal volume ventilatory strategy improves outcome in persistent acute respiratory distress syndrome: A randomized, controlled trial*

Jesús Villar, MD, PhD, FCCM; Robert M. Kacmarek, PhD, FCCM; Lina Pérez-Méndez, MD, PhD; Armando Aguirre-Jaime, PhD; for the ARIES Network

- Set ventilator based on PV curves
- Similar to Amato's strategy

Table 2. Main outcome variables

	Control	P_{flex}/LTV	*p* Value
Ventilator-free days	6.0 ± 7.9	10.9 ± 9.4	.008
Barotrauma, n (%)	4 (8.4)	2 (4)	.418
No. of organ failures: post-pre randomization	1.2 (0.7–1.6)	0.3 (0–0.7)	<.001
ICU mortality rate, %	53.3	32.0	.040

P_{flex}, lower inflection point of the pressure volume curve of the respiratory system; LTV, low tidal volume; ICU, intensive care unit.

- one protocol violation kept this out of NEJM

CCM May 2006

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 13, 2008 VOL. 359 NO. 20

Mechanical Ventilation Guided by Esophageal Pressure in Acute Lung Injury

Daniel Talmor, M.D., M.P.H., Todd Sarge, M.D., Atul Malhotra, M.D., Carl R. O'Donnell, Sc.D., M.P.H., Ray Ritz, R.R.T., Alan Lisbon, M.D., Victor Novack, M.D., Ph.D., and Stephen H. Loring, M.D.

Table 4. Clinical Outcomes.*

Outcome	Esophageal-Pressure–Guided (N=30)	Conventional Treatment (N=31)	P Value
28-Day mortality — no. (%)	5 (17)	12 (39)	0.055
180-Day mortality — no. (%)	8 (27)	14 (45)	0.13
Length of ICU stay — days			0.16
Median	15.5	13.0	
Interquartile range	10.8–28.5	7.0–22.0	

Transpulmonary Pressure

- Transpulmonary pressure (P_L) is the pressure actually distending the lung.

$$P_L = P_{ao} - P_{pl}$$

- Knowing pleural pressure (P_{pl}) could allow calculation of transpulmonary pressure (P_L) to individualize pressures appropriate to the lungs.

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.

CONCLUSIONS

We found that ΔP was the ventilation variable that best stratified risk. Decreases in ΔP owing to changes in ventilator settings were strongly associated with increased survival. (Funded by Fundação de Amparo e Pesquisa do Estado de São Paulo and others.)

NEJM 2015

Critique of Amato et al.

- Driving pressure independent of tidal volume predictive value is surprising if not implausible
- Statistics were robust but complex
- Primary studies had relatively fixed tidal volume diminishing its predictive value

Driving Pressure and Respiratory Mechanics in ARDS

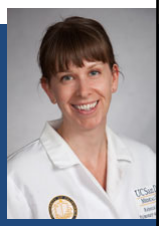
Stephen H. Loring, M.D., and Atul Malhotra, M.D.

- Plateau pressure minus PEEP predicts mortality in lots of different trials
- Incorporates scaling based on lung compliance
- Still emphasize importance of transpulmonary pressure in determining lung stress

NEJM 2015

EDITORIAL

Acute respiratory distress syndrome and the promise of driving pressure



- Limiting driving pressure may help in preventing ARDS (Blondonnet et al.)
- Caution if spontaneous breathing
- Raising PEEP is not the same as lowering tidal volume even though similar driving pressure
- Tidal recruitment may maximize atelectrauma but could lower driving pressure

Respirology in press

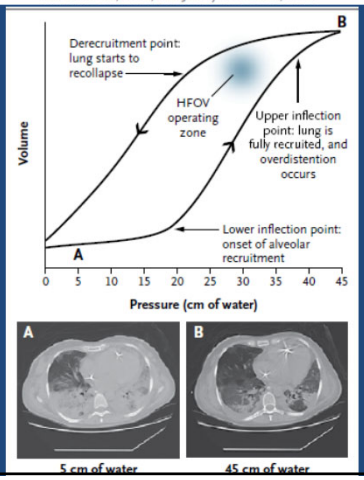
Rebecca E. Sell, MD and Atul Malhotra, MD
Division of Pulmonary and Critical Care Medicine, Department of Medicine, University of California San Diego, San Diego, CA, USA

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIAL

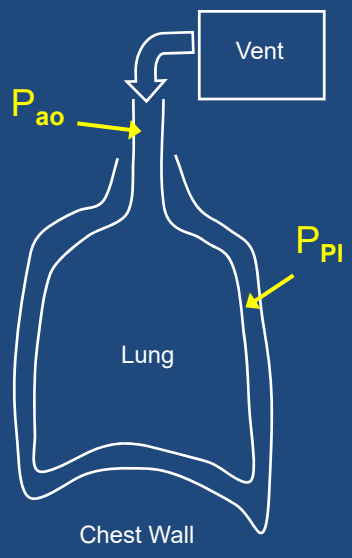
High-Frequency Oscillatory Ventilation on Shaky Ground

Atul Malhotra, M.D., and Jeffrey M. Drazen, M.D.



NEJM 2013

Did Prior Studies Use the Right Target?

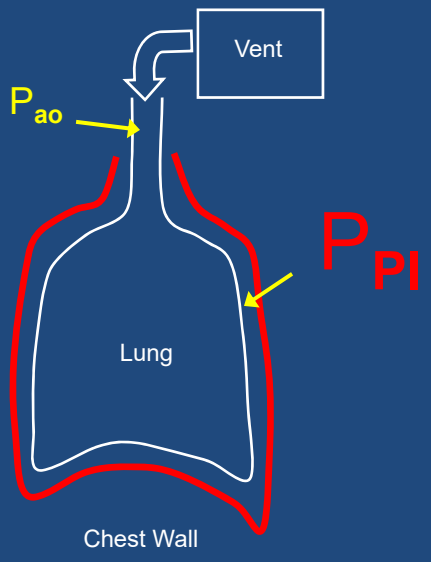


$$P_L = P_{ao} - P_{PI}$$

P_L is the pressure actually distending the lung.

This may be very different from the pressure measured at the airway.

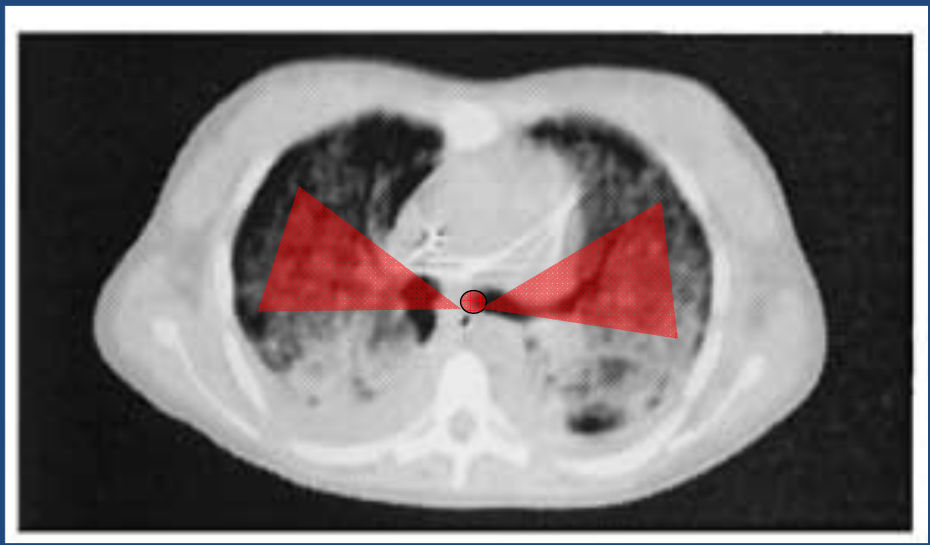
P_L May be Very Different then P_{ao}



$$P_L = P_{ao} - P_{PI}$$

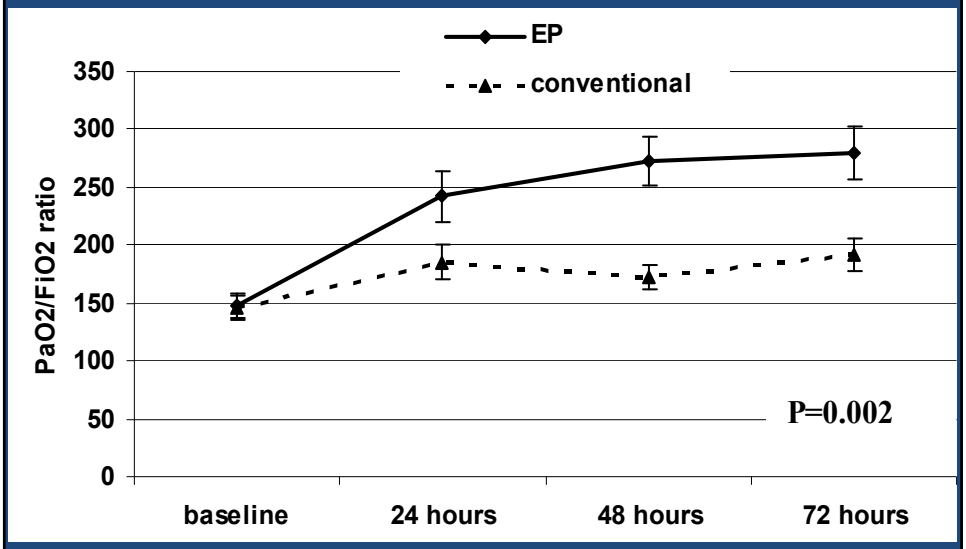
Titrating ventilation based on ventilator pressures does not allow us to take this variability into account

In Humans

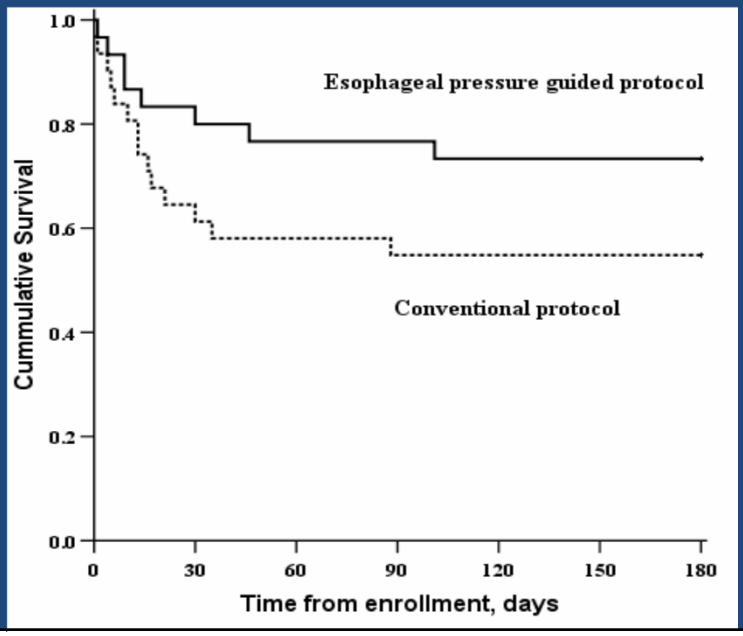


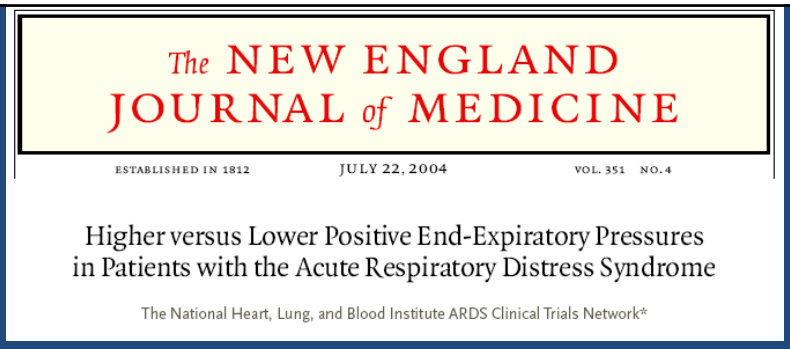
Gattinoni. Am J Respir Crit Care Med Vol 164. pp 1701–1711, 2001

Patient Oxygenation- Repeated Measures



6- Month Survival





- **Studied high vs. low PEEP and showed no difference**
- **PEEP set based on oxygenation tables which were reasonably arbitrary.**

NEJM July 2004

Clinical Trial Oxygenation vs. Mechanics

Oxygenation
ALVEOLI - negative
LOVS - negative
Mechanics
Amato - positive
Villar - positive
EpVent - positive

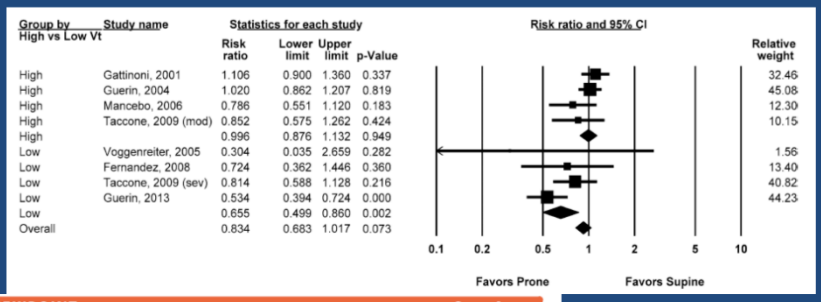
? Express - equivocal

Intensive Care Med (2014) 40:332–341
DOI 10.1007/s00134-013-3194-3

SYSTEMATIC REVIEW

Jeremy R. Beitler
Shahzad Shaefi
Sydney B. Montesi
Amy Devlin
Stephen H. Loring
Daniel Talmor
Atul Malhotra

Prone positioning reduces mortality from acute respiratory distress syndrome in the low tidal volume era: a meta-analysis



VIEWPOINT Open Access

PEEP titration during prone positioning for acute respiratory distress syndrome

Jeremy R. Beitler[1*], Claude Guérin[2,3], Louis Ayzac[4], Jordi Mancebo[5], Dina M. Bates[1], Atul Malhotra[1] and Daniel Talmor[6]

ICM 2014, Crit Care 2015

Prone positioning in acute respiratory distress syndrome: why aren't we using it more?

Mark L. Hepokoski, Mazen Odish, Atul Malhotra

- Convenience
- Debate over mechanism
- Likely not just a function of paralytics
- Patient ventilator synchrony may be important
- It may be the only thing that works !

JTD 2018

Effect of Lung Recruitment and Titrated Positive End-Expiratory Pressure (PEEP) vs Low PEEP on Mortality in Patients With Acute Respiratory Distress Syndrome
A Randomized Clinical Trial
Writing Group for the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial (ART) Investigators, Alexandre Biasi Cavalcanti, MD, PhD, [...], and Carlos Roberto Ribeiro de Carvalho, MD, PhD

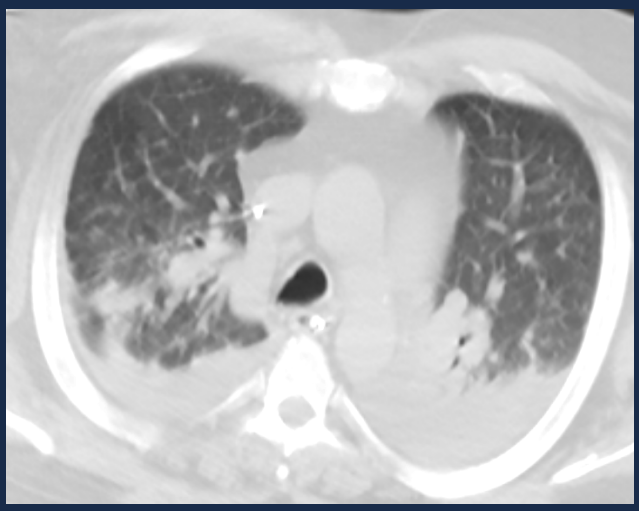
Increased mortality using strategy I recommend

Ouch

Maybe some design flaws e.g. best compliance

JAMA 2017

Rethinking the ARDS Lung



46

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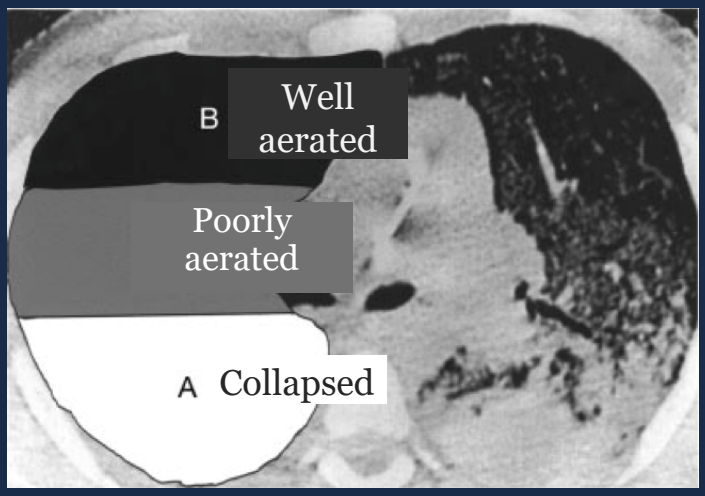
Ventilator-induced Lung Injury

Jeremy R. Beitler, MD, MPH[a,*], Atul Malhotra, MD[b], B. Taylor Thompson, MD[b]

Clinics Chest Medicine 2016

The ARDS "Baby Lung"



47

Figure from: Moloney. *Br J Anaeth.* 2004;92:261-270.

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Baby Lung: Implications for Lung Injury

• **Well-aerated regions**	Risk of overdistension (volutrauma/barotrauma)
• **Poorly aerated regions**	Risk of cyclic atelectasis
• **Collapsed regions**	Decrease lung volume available for ventilation
• **Inhomogeneity (border zones)**	High shear forces

Best evidence: therapies targeting optimal mechanics

48

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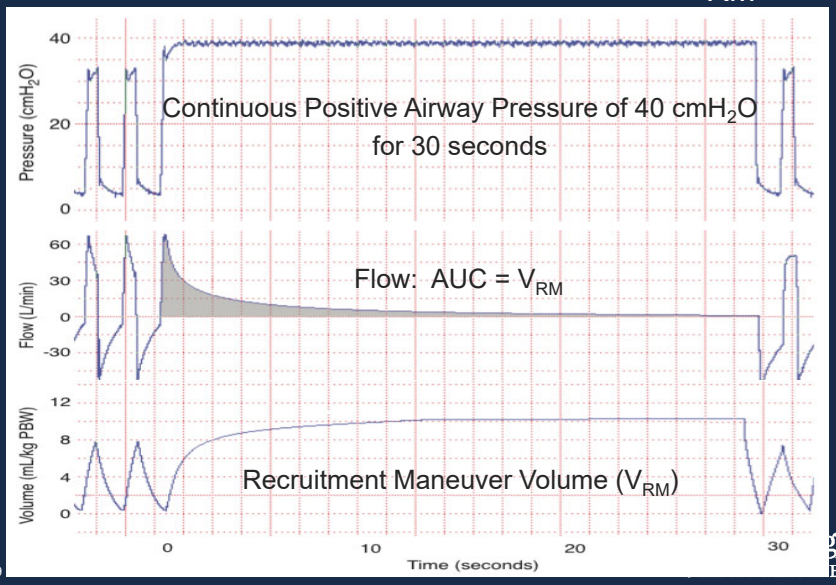
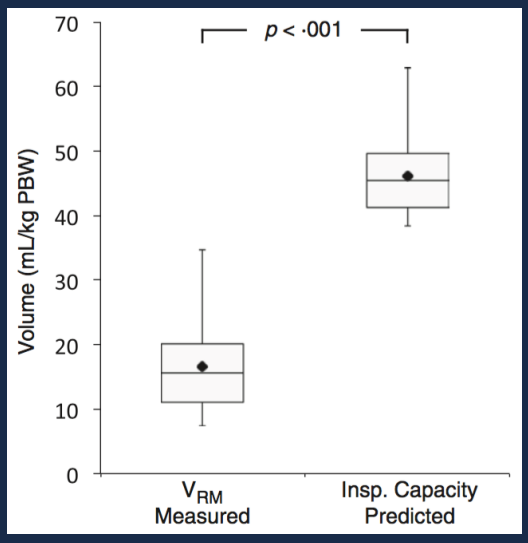
Recruitment Maneuver Volume (V_{RM})



49

Beitler et al. *Crit Care Med.* 2016;44:91-99

Recruitment Maneuver Volume (V_{RM})



50

Beitler et al. *Crit Care Med.* 2016;44:91-99

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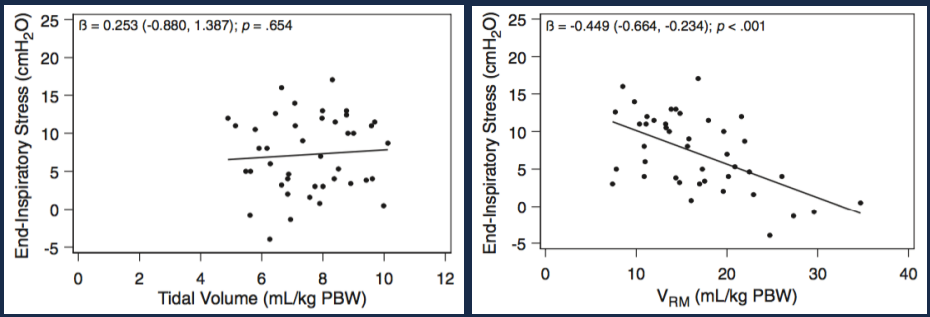
Predicting Lung Stress & Mortality

- End-inspiratory stress: Ptp = Paw – Ppl



- V_{RM} predicts risk of death (OR 0.84, 95% CI 0.71-1.00; p = .02)

51

Beitler et al. *Crit Care Med.* 2016;44:91-99

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V_T/V_{RM}: Scaling V_T to Baby Lung Size

- V_{RM} = maximum insufflation volume achievable under clinically plausible conditions
  - Analogous to relative inspiratory capacity measured beginning from PEEP
- V_T/V_{RM} = fraction of the potentially available lung volume that is insufflated with each tidal breath

52

Beitler et al. *Crit Care Med.* 2016;44:91-99

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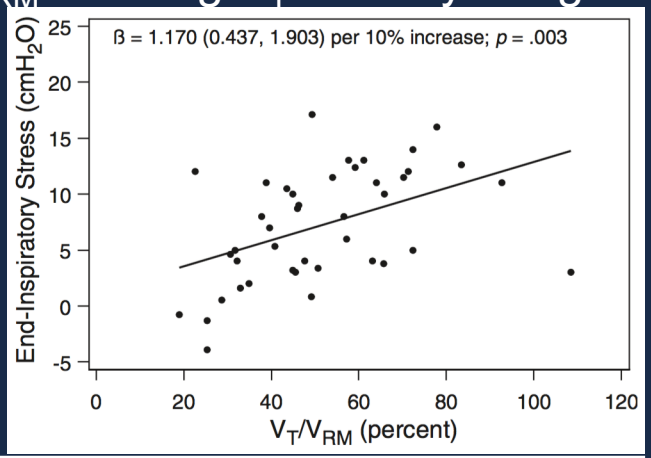
V_T/V_{RM}: Scaling V_T to Baby Lung Size



Volume Delivered During Recruitment Maneuver Predicts Lung Stress in Acute Respiratory Distress Syndrome*

Jeremy R. Beitler, MD, MPH[1]; Rohit Majumdar, BS[2]; Rolf D. Hubmayr, MD[3]; Atul Malhotra, MD[1]; B. Taylor Thompson, MD[4]; Robert L. Owens, MD[1]; Stephen H. Loring, MD[5]; Daniel Talmor, MD, MPH[5]

CCM 2016

San Diego
School of Medicine

Summary

- Oxygenation is one of many factors that influences ventilator settings
- Mechanics may be more important than oxygenation since patients rarely die from low PO2 and the goal is to do no mechanical harm with ventilator
- Multiple factors including individual's hemodynamics and mechanics should influence PEEP decisions as well as response to therapy (recruitability)
- We need more RCTs but small existing studies which have titrated ventilator settings based on lung and chest wall mechanics have succeeded.
- Providing tidal volume consistent with the available lung for gas exchange deserves further study
- EPVENT 2 and ROSE are soon to release

Disclosures /Funding

Grants PI: Malhotra

- NIH and AHA

Industry (none since May 2012)

REFRACTORY HYPOXEMIA

Joseph Levitt, MD, MSC
Stanford University
Assistant Professor of Medicine

Friday, January 18, 2019 – 10:45 a.m. – 11:35 a.m.

Joseph Levitt, MD, MSc, received his medical degree from the University of Minnesota. He did his resident training in Internal Medicine at the University of Chicago and fellowship training in Pulmonary and Critical Care Medicine at the University of Chicago and Stanford University. Dr. Levitt received an NIH Career Development Award to study the treatment of early Acute Lung Injury prior to onset of respiratory failure. He has been the site-Principal Investigator at Stanford for the ARDS Network and is the current site-PI for the NHLBI Network for the Prevention of Acute Lung Injury (PETAL). Dr. Levitt serves as an Assistant Professor of Medicine at Stanford University and the Program Director for the Pulmonary and Critical Care Medicine Fellowship.

REFRACTORY HYPOXEMIA: What is it and what can we do about it?

JOSEPH LEVITT, MD

CALIFORNIA THORACIC SOCIETY

JANUARY 18-19, 2019

CONFLICT OF INTEREST

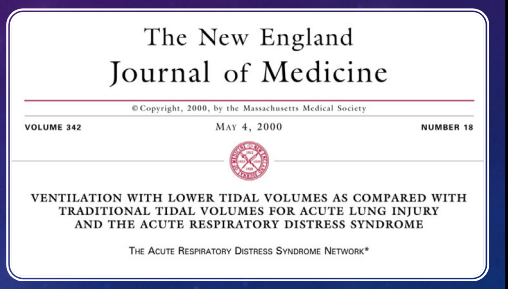
NONE

REFRACTORY HYPOXEMIA: WHAT IS IT?

Original ARDSNet Low Tidal Volume Trial

- Targeted SpO_2 88 – 95% or PaO_2 55 – 80 mmHg
- Treatment arm had lower PaO_2 but better survival

So it's not that!

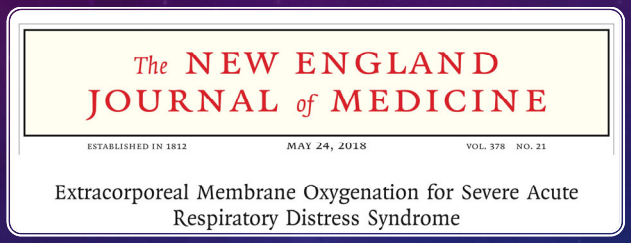

The New England Journal of Medicine

VOLUME 342 MAY 4, 2000 NUMBER 18

VENTILATION WITH LOWER TIDAL VOLUMES AS COMPARED WITH TRADITIONAL TIDAL VOLUMES FOR ACUTE LUNG INJURY AND THE ACUTE RESPIRATORY DISTRESS SYNDROME

THE ACUTE RESPIRATORY DISTRESS SYNDROME NETWORK*

REFRACTORY HYPOXEMIA: WHAT IS IT?


The NEW ENGLAND JOURNAL of MEDICINE

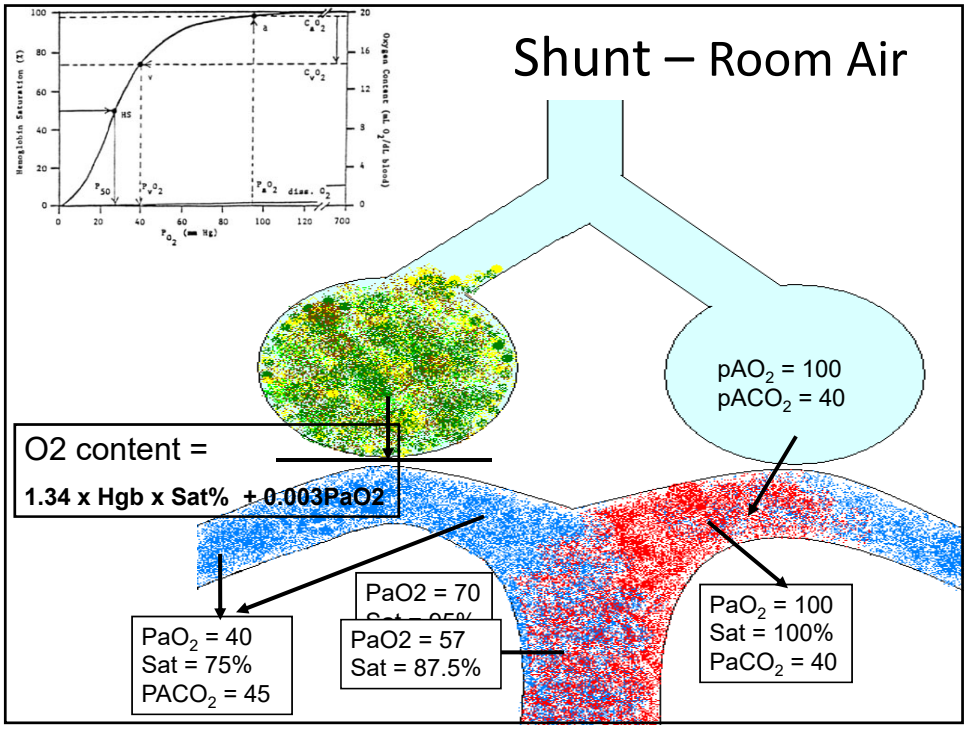
ESTABLISHED IN 1812 MAY 24, 2018 VOL. 378 NO. 21

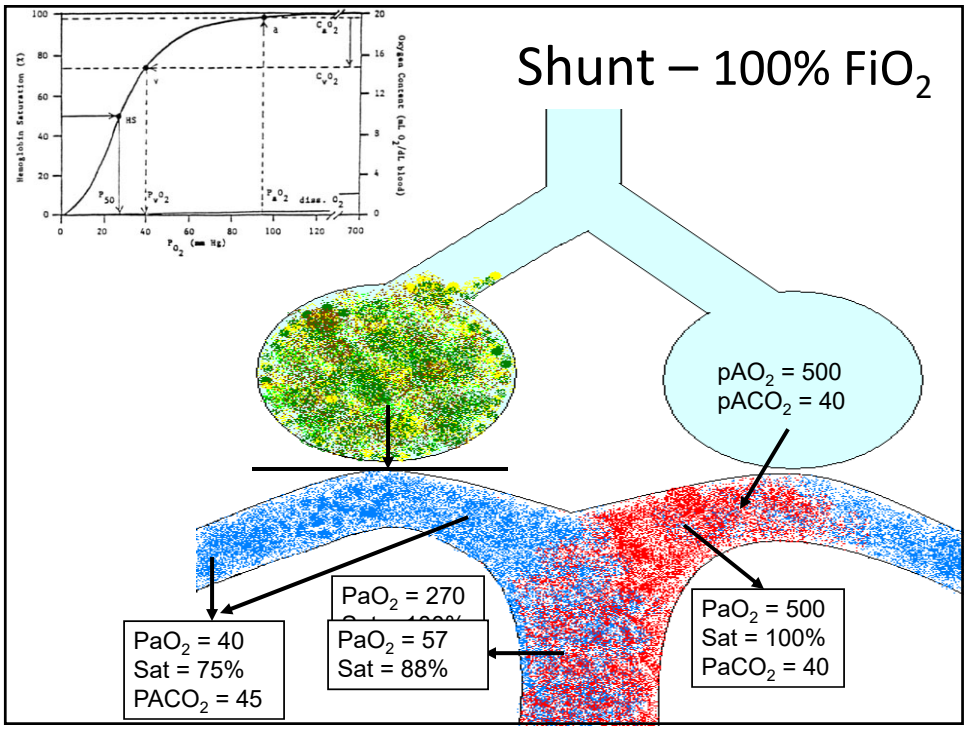
Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome

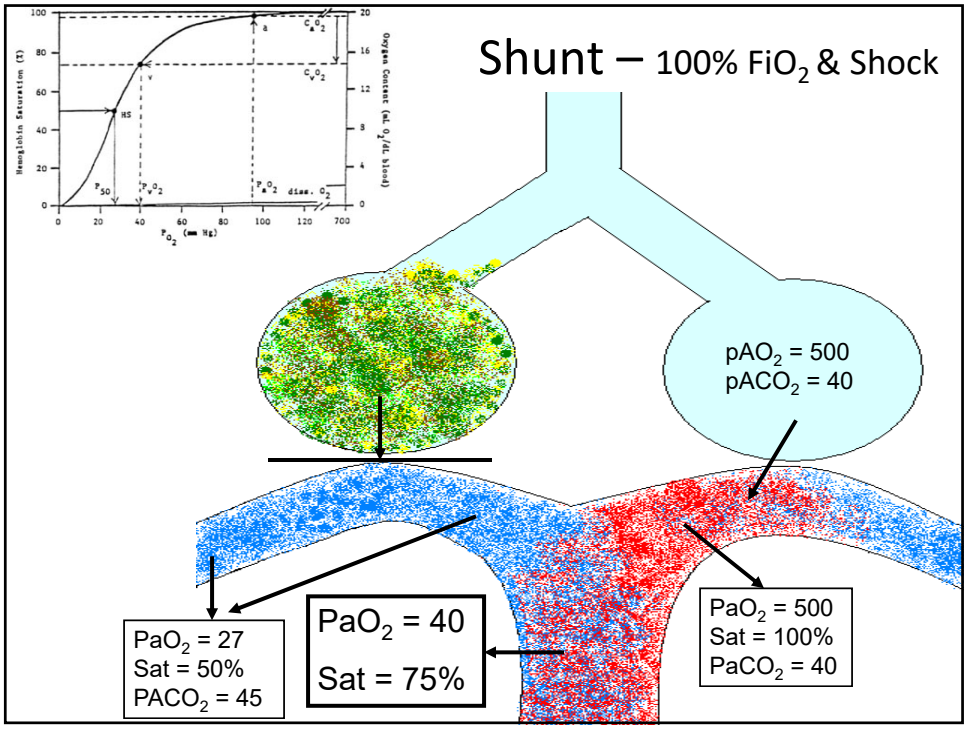
Recent EOLIA (ECMO) Trial

- Allowed crossover for SpO_2 < 80% for 6 hours
- 57% 60-day mortality despite receiving ECMO

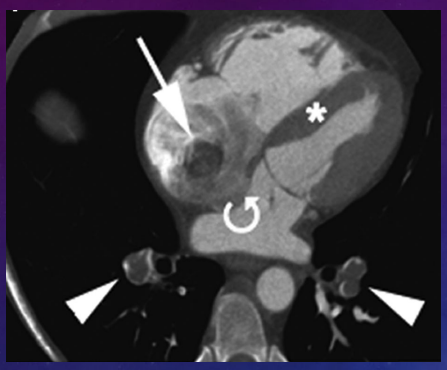
Can we agree that it is that?

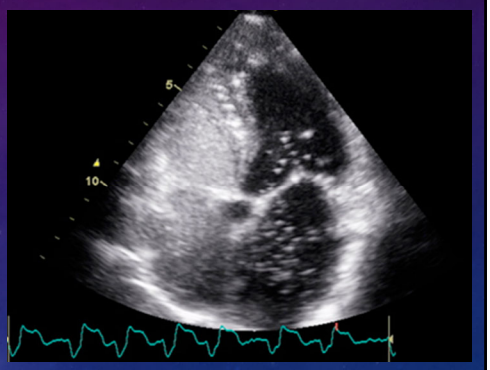

Shunt – Room Air
pAO2 = 100
pACO2 = 40
O2 content =
1.34 x Hgb x Sat% + 0.003PaO2
PaO2 = 70
PaO2 = 57
Sat = 87.5%
PaO2 = 40
Sat = 75%
PACO2 = 45
PaO2 = 100
Sat = 100%
PaCO2 = 40


Shunt – 100% FiO2
pAO2 = 500
pACO2 = 40
PaO2 = 270
PaO2 = 57
Sat = 88%
PaO2 = 40
Sat = 75%
PACO2 = 45
PaO2 = 500
Sat = 100%
PaCO2 = 40



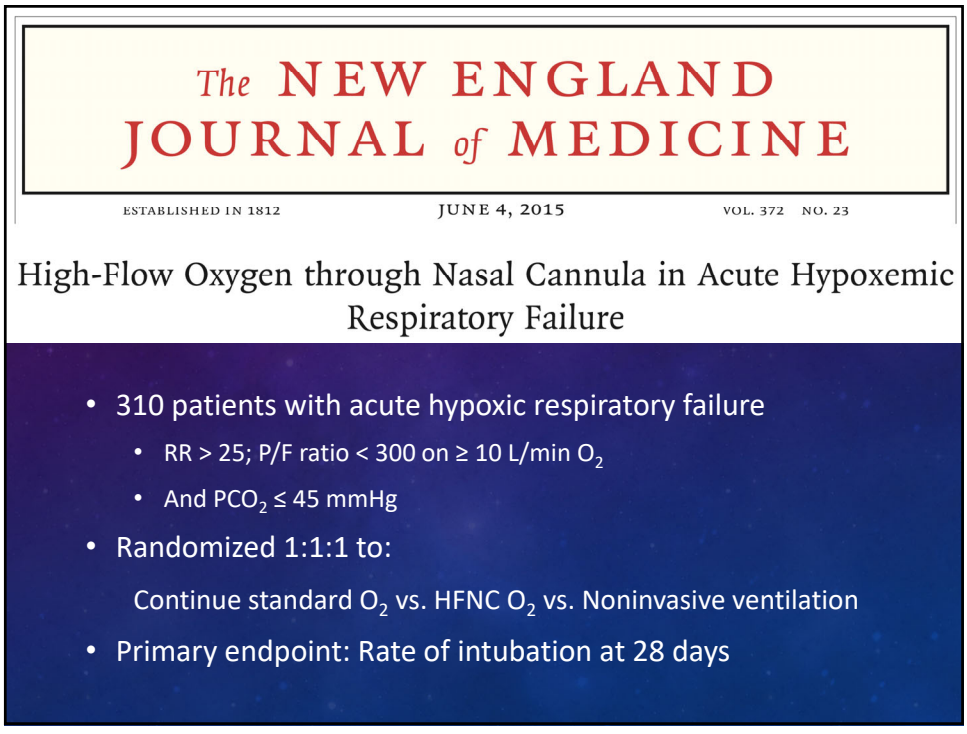
INTRACARDIAC SHUNT





- Submassive Pulmonary Embolism with R to L shunt through patent PFO (up to 30% of population)
  - Consider TPA for refractory hypoxemia


The NEW ENGLAND JOURNAL of MEDICINE
Effect of Recombinant Surfactant Protein C–Based Surfactant on the Acute Respiratory Distress Syndrome
JAMA The Journal of the American Medical Association
Low-Dose Inhaled Nitric Oxide in Patients With Acute Lung Injury
A Randomized Controlled Trial
Prone Positioning in Patients With Moderate and Severe Acute Respiratory Distress Syndrome
A Randomized Controlled Trial
Multicenter clinical trials that
Improved Oxygenation but
Failed to improve Mortality
ORIGINAL ARTICLE
Comparison of Two Fluid-Management Strategies in Acute Lung Injury
The NEW ENGLAND JOURNAL of MEDICINE
JULY 22, 2004
Higher versus Lower Positive End-Expiratory Pressures in Patients with the Acute Respiratory Distress Syndrome


The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812
JUNE 4, 2015
VOL. 372 NO. 23
High-Flow Oxygen through Nasal Cannula in Acute Hypoxemic Respiratory Failure
• 310 patients with acute hypoxic respiratory failure
• RR > 25; P/F ratio < 300 on ≥ 10 L/min O_2
• And PCO_2 ≤ 45 mmHg
• Randomized 1:1:1 to:
Continue standard O_2 vs. HFNC O_2 vs. Noninvasive ventilation
• Primary endpoint: Rate of intubation at 28 days

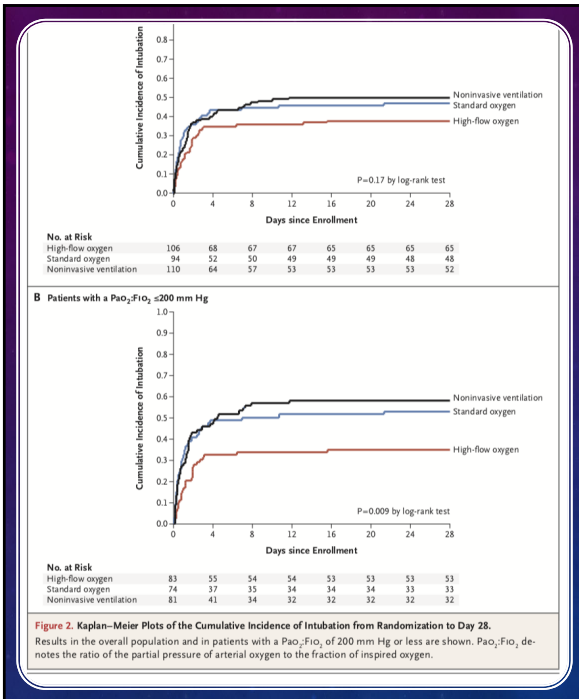


Figure 2. Kaplan–Meier Plots of the Cumulative Incidence of Intubation from Randomization to Day 28.
Results in the overall population and in patients with a PaO_2:FiO_2 of 200 mm Hg or less are shown. PaO_2:FiO_2 denotes the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen.

HIGH-FLOW OXYGEN

- Trend toward reduced intubations
- Significant reduction in intubation rate if P/F < 200 …
- But, post-hoc analysis

Table 2. (Continued.)

Outcome	Study Group			P Value†	Odds Ratio or Hazard Ratio (95% CI)	
	High-Flow Oxygen (N=106)	Standard Oxygen (N=94)	Noninvasive Ventilation (N=110)		Standard Oxygen vs. High-Flow Oxygen	Noninvasive Ventilation vs. High-Flow Oxygen
Death						
In ICU						
Unadjusted analysis				0.047	1.85 (0.84–4.09)	2.55 (1.21–5.35)
No. of patients	12	18	27			
% of patients (95% CI)	11 (6–19)	19 (12–28)	25 (17–33)			
Adjusted analysis**	—	—	—	—	2.55 (1.07–6.08)	2.60 (1.20–5.63)
At day 90						
Overall p						
Unad				0.02	2.01 (1.01–3.99)	2.50 (1.31–4.78)
N						
% of patients (95% CI)	12 (7–20)	23 (16–33)	28 (21–37)			
Adjusted analysis**	—	—	—	—	2.36 (1.18–4.70)	2.33 (1.22–4.47)
Intubated patients				0.16		
No. of patients/total. no.	12/40	20/44	27/55			
% of patients (95% CI)	30 (18–46)	45 (32–60)	49 (36–62)			
Cause of death — no./total no. (%)						
Refractory shock	6/13 (46)	12/22 (55)	18/31 (58)	0.04		
Refractory hypoxemia	5/13 (38)	6/22 (27)	8/31 (26)	0.73		
Cardiac arrest	1/13 (8)	1/22 (5)	3/31 (10)	0.52		
Other	1/13 (8)	3/22 (14)	2/31 (6)	0.52		

2.36 (1.18–4.70) 2.33 (1.22–4.47)

HIGH-FLOW NASAL CANNULA OXYGEN

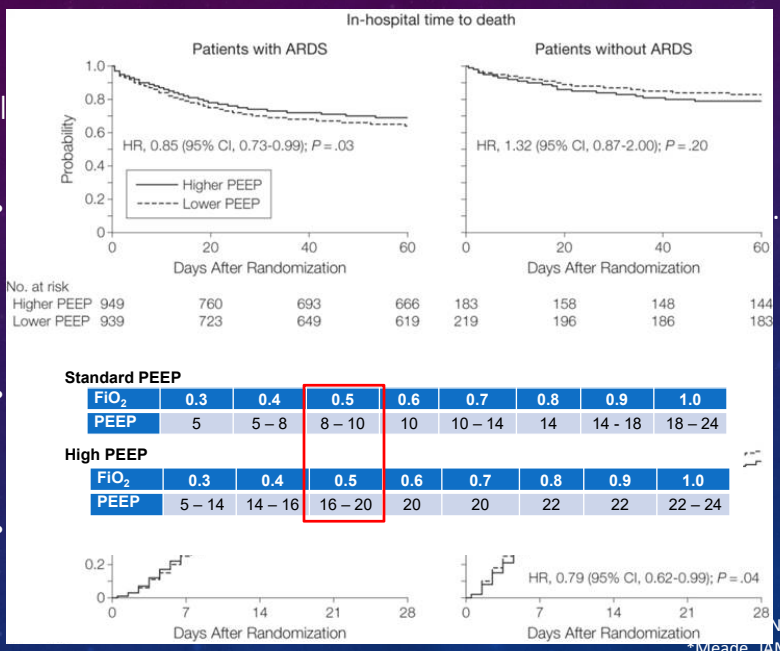
- More comfortable and better tolerated
- Allows ongoing enteral nutrition and communication
- Likely reduces need for invasive mechanical ventilation and may increase survival
  - Likely reduces dead space +/- benefit of minimal PEEP
- Should probably be 1st treatment for refractory hypoxemia
- Noninvasive ventilation should be reserved for hypercapnic respiratory failure or CHF

PULMONARY VASCULAR VASODILATORS

- Inhaled Nitric Oxide and Prostacyclin (Epoprostenol) consistently shown to:
  - Reduce pulmonary vascular resistance
  - Transiently improve oxygenation
- But, no survival benefit or shorter time to extubation
  - Generally not recommended for treatment of ARDS
- But, Epoprostenol much cheaper than iNO and may have benefit in select cases
  - < 20% Mortality from ARDS due to refractory hypoxemia*

*Stapleton et al, Chest 2005

HI



Standard PEEP

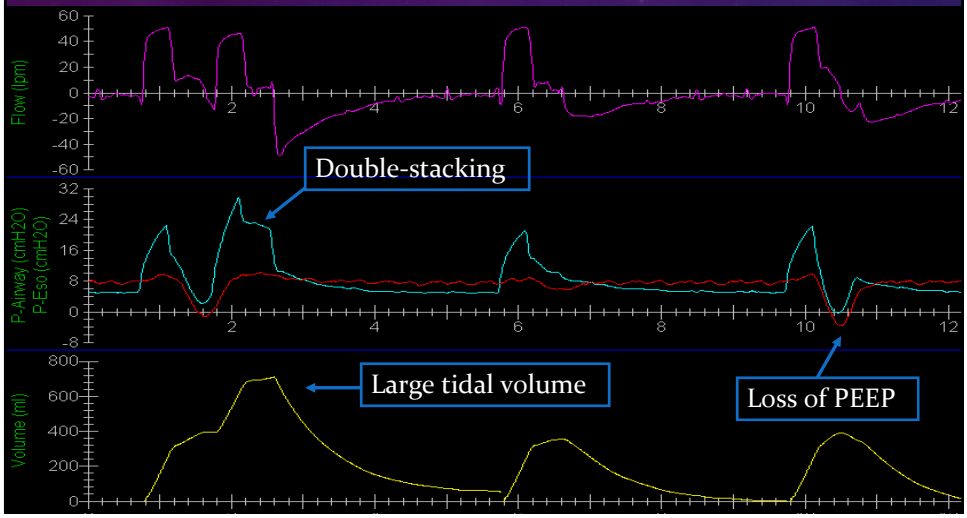
FiO_2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
PEEP	5	5 – 8	8 – 10	10	10 – 14	14	14 - 18	18 – 24

High PEEP

FiO_2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
PEEP	5 – 14	14 – 16	16 – 20	20	20	22	22	22 – 24

NEJM 2004
*Meade, JAMA 2008
#EXPRESS, JAMA 2008

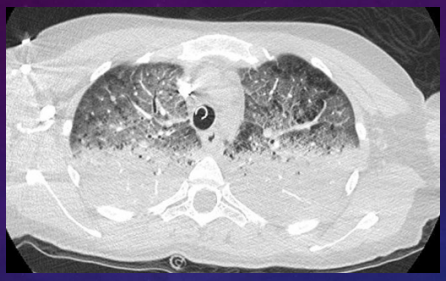
PATIENT-VENTILATOR DYSSYNCHRONY WITH LUNG-PROTECTIVE VENTILATION



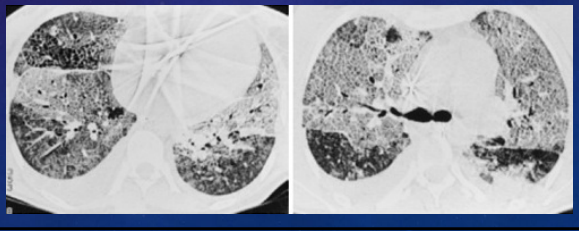
NEUROMUSCULAR BLOCKADE (PARALYSIS)

- 340 patient RCT ARDS (P/F < 150) Paralysis vs. Heavy Sedation (Ramsay Score 6 both arms)
  - Overall mortality benefit (primarily with P/F < 120)
  - Higher P/F at 7 days but not 24 and 72 hours
- Re-Evaluation of Systemic Early Neuromuscular Blockade (ROSE)
  - 1400 patient PETAL Network trial
  - Stopped early at 1000 patients (results pending)

BASELINE IN SUPINE POSITION

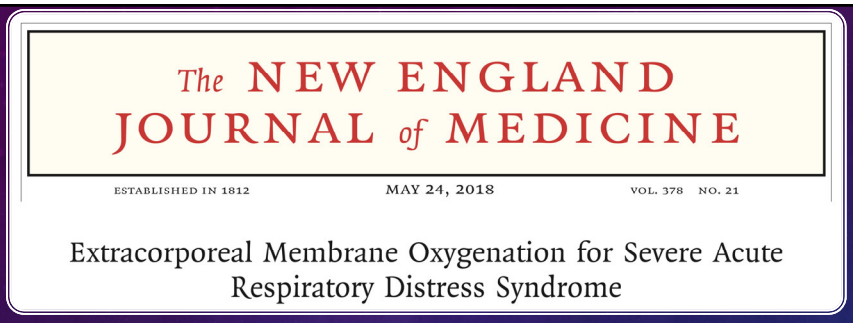


AFTER 12 HOURS IN PRONE POSITION



PRONE POSITIONING

- 2 large RCT's (Guerin, JAMA 2004; Taccone JAMA 2009)
  - Improved oxygenation
  - No mortality benefit
- Meta-analysis 1867 patients (Gattinoni AJRCCM 2010)
  - Lower mortality in patients with P/F < 100
- Most recent RCT (Guerin NEJM, 2013)
  - 466 pts w/ severe ARDS (P/F < 150 on FiO_2 > 0.6)
  - Reduced mortality (16% vs. 33%, P<0.001)
  - No increased complications from proning
  - ARDSNet Low PEEP protocol for both groups



- 249 patients with:
  - P/F < 50 for > 3 hours or < 80 for > 6 hours OR
  - pH < 7.25 and PCO2 > 60 mmHg AND
  - FiO2 ≥ 80% and PEEP ≥ 10 mmHg
  - Proning and paralysis encouraged before enrollment
- Randomized to ECMO or Express trial (High PEEP) protocol
- Cross-over allowed if SpO2 < 80 for 6 hours and no irreversible multiorgan failure

EOLIA TRIAL

- Stopped early for futility (249 of 331 pts)
- 60-day Mortality 35% vs 46% (p = 0.09)

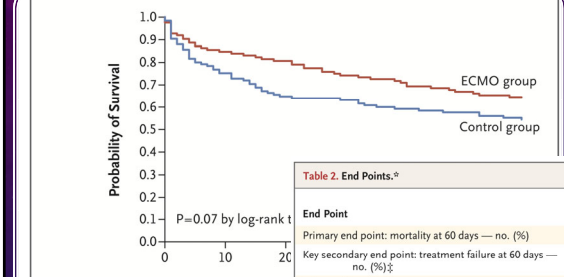
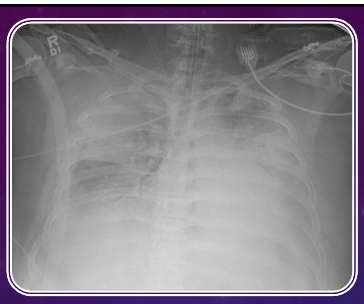


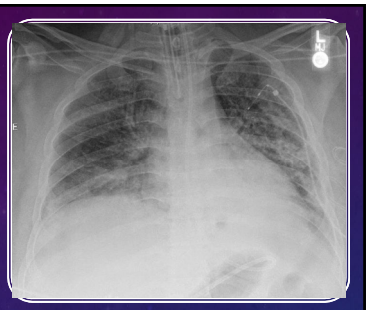
Figure 2. Kaplan–Meier Survival Estir
tion during the First 60 Days of the T

Table 2. End Points.*

End Point	ECMO Group (N=124)	Control Group (N=125)	Relative Risk or Difference (95% CI)†	P Value
Primary end point: mortality at 60 days — no. (%)	44 (35)	57 (46)	0.76 (0.55 to 1.04)	0.09
Key secondary end point: treatment failure at 60 days — no. (%)‡	44 (35)	72 (58)	0.62 (0.47 to 0.82)	<0.001
Other end points				
Mortality at 90 days — no. (%)	46 (37)	59 (47)	−10 (−22 to 2)	
Median length of stay (interquartile range) — days				
In the ICU	23 (13–34)	18 (8–33)	5 (−1 to 10)	
In the hospital	36 (19–48)	18 (5–43)	18 (6 to 25)	
Median days free from mechanical ventilation (interquartile range)§	23 (0–40)	3 (0–36)	20 (−5 to 32)	
Median days free from vasopressor use (interquartile range)§	49 (0–56)	40 (0–53)	9 (0 to 51)	
Median days free from renal-replacement therapy (interquartile range)§	50 (0–60)	32 (0–57)	18 (0 to 51)	
Prone position — no. (%)¶	82 (66)	113 (90)	−24 (−34 to −14)	
Recruitment maneuvers — no. (%)¶	27 (22)	54 (43)	−21 (−32 to −10)	
Inhaled nitric oxide or prostacyclin — no. (%)¶	75 (60)	104 (83)	−23 (−33 to −12)	
Glucocorticoids — no. (%)¶	80 (65)	82 (66)	−1 (−13 to 11)	

DIURESIS





ARDSNet FACCT (NEJM 2006)

- Conservative vs. Liberal fluid strategy
- Improvement in Oxygenation Index but not P/F ratio (higher PEEP in Liberal fluid arm)
- Shorter duration of mechanical ventilation

CONCLUSIONS

- Important to distinguish **clinically-relevant refractory hypoxemia**
  - Consider intracardiac shunt
- High-Flow Nasal Cannula Oxygen should be 1st line
  - Noninvasive ventilation reserved for hypercapnia or CHF
- 3 P's of LPV
  - PEEP, proning, and paralysis
- ECMO improves survival
  - Likely 10 – 30% absolute risk reduction in select patients

Stanford MEDICINE

QUESTIONS?

JOSEPH LEVITT, MD

CALIFORNIA THORACIC SOCIETY

JANUARY 18-19, 2019

PRE-TEST QUESTION 1

A 50 y.o. previously healthy female is admitted to the ICU for pneumonia and sepsis. She is intubated for hypoxemic respiratory failure after failing a trial of HFNC O_2. Post-intubation CXR shows bilateral infiltrates. Current ventilator settings are AC with a 6 cc/kg TV PBW, RR of 30, PEEP 10 cmH_20, FiO_2 0.70 with a plateau pressure (Ppl) of 29 cmH_2O. Current SpO_2 is 90% with an ABG of 7.36/PaO_2 60/$PaCO_2$ 45/$HCO3^-$ 24. Evidence-based treatment strategies include:

A. Initiate neuromuscular blockade with cisatricurium
B. Initiate prone positioning for 16 hours per day
C. Increase PEEP to 20 cmH_20 and decrease TV to 4 cc/Kg PBW as necessary to keep Ppl < 35 cmH_20
D. Continue current ventilator settings without change
E. B,C, and D
F. All of the above

PRE-TEST QUESTION 2

2 days later the same patient is now paralyzed on AC with RR 35, TV 4 cc/kg, PEEP 22, FiO_2 1.0, Ppl of 32 cmH_20 with an ABG of pH 7.25/PaO_2 54/$PaCO_2$ 52/$HCO3^-$ 20. Her MAP is 65 mmHg on norepinephrine 10 mg/min and vasopressin 0.04 u/hr. Her CVP is 8 mmHg with a $ScVO_2$ of 72% without signs of volume overload. Her serum Cr has doubled to 2.5 mg/dL in 48 hours, but she has no other evidence of irreversible organ failure. Evidence-based treatment strategies include:

A. Start inhaled Epoprostenol at 20 ng/kg/min
B. Start diuresis with iv furosemide to achieve a CVP of ≤ 4 mmHg
C. Initiate prone positioning for 16 hours/day with consideration for starting ECMO if not improved in 24 hours
D. Repeat ABG in 6 hours and initiate cannulation for venovenous ECMO if PaO_2 still < 80 mmHg
E. C and D

POST-TEST QUESTION 1

A 50 y.o. previously healthy female is admitted to the ICU for pneumonia and sepsis. She is intubated for hypoxemic respiratory failure after failing a trial of HFNC O_2. Post-intubation CXR shows bilateral infiltrates. She appears comfortable on ventilator settings of AC with a 6 cc/kg TV PBW, RR of 30, PEEP 10 cmH_20, FiO_2 0.70 with a plateau pressure (Ppl) of 29 cmH_2O. Current SpO_2 is 90% with an ABG of 7.36/PaO_2 60/$PaCO_2$ 45/$HCO3^-$ 24. Evidence-based treatment strategies include:

A. Initiate neuromuscular blockade with cisatricurium for 48 hours
B. Initiate prone positioning for 16 hours per day
C. Increase PEEP to 20 cmH_20 and decrease TV to 4 cc/Kg PBW as necessary to keep Ppl < 35 cmH_20
D. Continue current ventilator settings without change
E. B,C, and D
F. All of the above

ANSWER 1

The patient is currently meeting target SpO_2 of 88-95% or PaO_2 of 55-80 mmHg on ARDSNet LPV settings with standard PEEP. Changes to ventilator settings with sole goal of improving oxygenation are unnecessary and could be harmful. While no RCT has shown high PEEP to be improve survival relative to current settings, a meta-analysis of 3 large trials suggested benefit of high PEEP for patients with a P/F ratio < 200. Additionally, RCT's have suggested benefit for 48 hours of neuromuscular blockade with cisastricurium as well as for prone positioning for patients with a P/F < 150 on 10 cmH_20 of PEEP. However, some equipoise remains regarding benefit of these additional therapies in patients adequately treated with standard LPV. Therefore, F (All of the above) is the best answer.

PRE-TEST QUESTION 2

2 days later the same patient is now paralyzed on AC with RR 35, TV 4 cc/kg, PEEP 22, FiO_2 1.0, Ppl of 32 cmH_20 with an ABG of pH 7.25/PaO_2 54/$PaCO_2$ 52/$HCO3^-$ 20. Her MAP is 65 mmHg on Norepinephrine 10 mg/min and vasopressin 0.04 u/hr. Her CVP is 8 mmHg with a $ScVO_2$ of 72% without signs of volume overload. Her serum Cr has doubled to 2.5 mg/dL in 48 hours, but she has no other evidence of irreversible organ failure. Evidence-based treatment strategies include:

A. Start inhaled Epoprostenol at 20 ng/kg/min

B. Start diuresis with iv furosemide to achieve a CVP of ≤ 4 cmH20

C. Initiate prone positioning for 16 hours/day with consideration for starting ECMO if not improved in 24 hours

D. Repeat ABG in 6 hours and initiate cannulation for venovenous ECMO if PaO_2 still < 80 mmHg

E. C and D

ANSWER 2

Despite management with standard ARDSNet LPV, the patients condition has progressed and she has been appropriately paralyzed and placed on High PEEP. However, she is not currently meeting her oxygenation target (PaO_2 55-80) and now has clinically relevant refractory hypoxemia. Starting inhaled Epoprostenol would likely lead to a transient improvement in oxygenation, however she does not appear to have an rapidly reversible cause of her hypoxemia and Epoprostenol is unlikely to change her overall outcome (A is incorrect). While the ARDSNet FACTT trial supports a conservative fluid strategy targeting a CVP ≤ 4 mmHg, the protocol only applied after resolution of shock. The patient currently has an intermediate level CVP on vasopressors with a rising Cr. Diuresis would not likely be helpful unless evidence of significant volume overload is present (B is incorrect). The patient currently meets criteria for a trial of prone positioning, especially if not currently at a center with expertise in ECMO. However, she is failing current standard therapy and is otherwise healthy without irreversible organ damage and would likely benefit from venovenous ECMO if she has a P/F ratio persistently < 80 for 6 hours per the recent EOLIA trial inclusion criteria. Therefore, E (C and D) is the best answer.

LARGE GROUP: VENTILATOR MANAGEMENT 1
Ventilator Graphics, Scalars, Lung Mechanics (ASL 5000 with vent)

Friday, January 18, 2019 – 11:35 a.m. – 12:05

Lance Pangilinan, RRT
UC San Francisco
Adult Critical Care Respiratory Therapist

Lance Pangilinan, RRT, is an Adult Critical Care Respiratory Therapist for the University of California San Francisco, Department of Anesthesia at Zuckerberg San Francisco General Hospital and Trauma Center (ZSFG). There, he currently serves as a bedside therapist and educator. Lance is a lecturer for the Critical Care Residency Program at ZSFG on the topics of Mechanical Ventilation Mechanics and ARDS management. He is a published researcher and has spoken nationally at a number of respiratory and critical care conferences on the subjects of strategic ventilation practices and the use of non-invasive end-tidal monitoring.

Justin Phillips, RRT
UC San Francisco
Adult Critical Care Respiratory Therapist

Justin Phillip, RRT, is an Adult Critical Care Respiratory Therapist for the University of California San Francisco, Department of Anesthesia at Zuckerberg San Francisco General Hospital and Trauma Center (ZSFG). There, he currently serves as a bedside therapist and educator. Justin is a lecturer for the Critical Care Residency Program at ZSFG on the topics of Mechanical Ventilation Mechanics and ARDS management. Additionally, he is Adjunct Faculty for the Respiratory Care Program at Ohlone College for Health Sciences and Technology. Justin is a published researcher and has spoken nationally at a number of respiratory and critical care conferences on the subjects of strategic ventilation practices and the use of non-invasive end-tidal monitoring.

Gregory Burns, RRT
UC San Francisco
Respiratory Care Practitioner

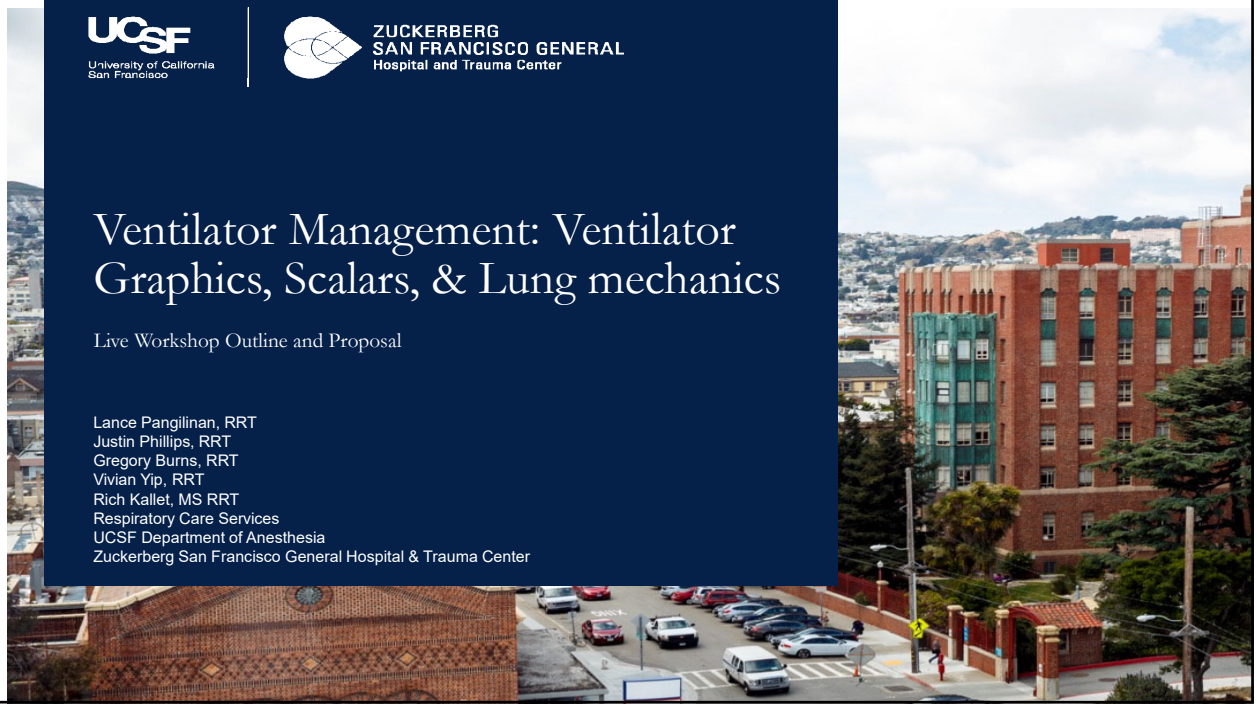
Gregory Burns, RRT, is a Respiratory Care Practitioner for the University of California San Francisco, Department of Anesthesia at Zuckerberg San Francisco General Hospital and Trauma Center (ZSFG). There, he currently serves as interim Equipment Manager. Gregory's research interests include the effect of inhaled vasodilators on patients with the Acute Respiratory Distress Syndrome.

Vivian Yip, BS, RRTACCS
UC San Francisco
Adult and Neonatal Critical Care
Respiratory Therapist

Vivian Yip, BS, RRT-ACCS, is a Adult and Neonatal Critical Care Respiratory Therapist for the University of California San Francisco, Department of Anesthesia at Zuckerberg San Francisco General Hospital and Trauma Center (ZSFG). There, she currently serves as a bedside therapist and educator. Vivian is a lecturer for the Critical Care Residency Program at ZSFG on the topics of Mechanical Ventilation Mechanics and ARDS management. Vivian is a published researcher and has spoken at a number of respiratory and critical care conferences on the subjects of spontaneous breathing trials and the impact of THAM in patients with severe acidosis in ARDS.

Rich Kallet, MS, RRT
UC San Francisco
Respiratory Therapist

Rich Kallet, MS, RRT received his baccalaureate degree in respiratory therapy from SUNY Upstate Medical University in Syracuse NY and his masters of sciences degree in health sciences from San Francisco State University. He spent the majority of his 42 year career working for the University of California, San Francisco Department of Anesthesia at San Francisco General Hospital and the UCSF Cardiovascular Research Institute. He was a research coordinator for NIH ARDS Network from 1996-2011 and has worked as a project manager and director of clinical research for the CVRI, the San Francisco Injury Center and both the Critical Care Management Group and the Respiratory Care Services at SFGH. He retired in 2018 and currently is section editor for the Respiratory Care Journal.



Overview

- Thirty (30) minute interactive panel discussion integrating live simulated clinical conditions via a high-fidelity lung model to a live audience
- Primary objectives include detailed discussion on Work of Breathing (WOB) and the intricacies of imposed work in various modes of mechanical ventilation

Overview

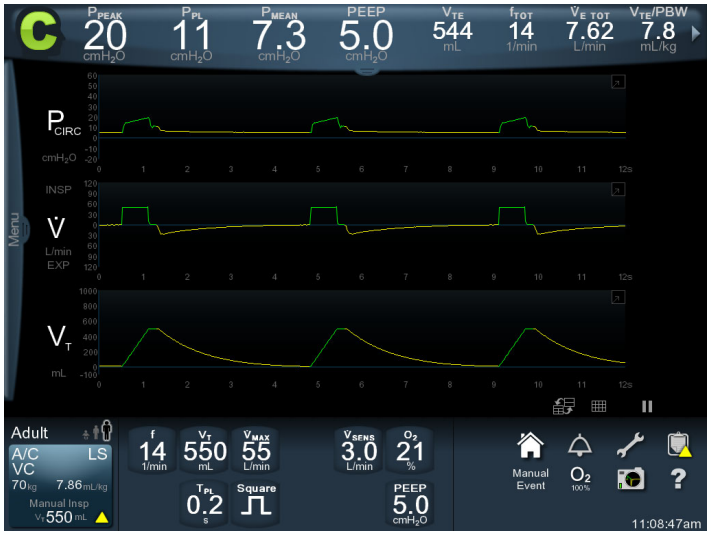
- Introduction to Scalars
- Partial vs. Full Support and WOB
- Volume vs. Pressure Targeted Ventilation Review
- WOB Under Intense Muscle Loading
- Dual Mode Ventilation Review

Introduction to Scalars

Introduction to Scalars

- Review of graphical layout of scalars
- The representation of time and…
  - Pressure
  - Flow
  - Volume

Introduction to Scalars



Partial vs. Full Support & WOB

Partial vs. Full Support & WOB

- **Teaching Points: Didactic**
  - Respiratory muscle loading
    - Three (3) loads
      - Resistive
      - Elastic
      - Threshold
        - Zero flow or chest displacement with diaphragm contraction secondary to intrinsic PEEP or trigger sensitivity threshold
  - Push-pull
    - Ventilator and patient work
      - Force x Distance **or** Pressure x Volume
    - Augments patient WOB

Partial vs. Full Support & WOB: Issues with Spontaneous Breathing

- **Teaching Points: Didactic**
  - Satisfying patient demand
    - Time Intervals
      - Breath initiation and termination
  - Clinician interpretation of V_T as an indicator for adequate support
    - The ability of PCV to lower patient WOB depends upon PC level
  - Preservation of minute ventilation
    - Determines effort (P_{MUS})

Partial vs. Full Support & WOB

- **Teaching Points: ASL 5000 Modeling**
  - ASL Settings
    1. Apnea
    2. Low work
  - A minimum mandatory rate that can be increased to augment V_E
    - Every breath controlled in terms of a fixed T_{INSP}
  - Partial support of minute ventilation demand
    - Uses patient's respiratory muscles to provide most of the power of breathing

Volume vs. Pressure Targeted Ventilation Review

Volume vs. Pressure Targeted Ventilation Review

- **Teaching Point: ASL 5000 Modeling**
  - ASL Settings: Low work
    1. High resistance
  - Vent Settings: Volume Control
- **Teaching Point: Didactic**
  - Circuit pressure is work required for ventilator to deliver set flow

Zuckerberg San Francisco General
UCSF

Volume vs. Pressure Targeted Ventilation Review

- **Teaching Point: ASL 5000 Modeling**
  - ASL Settings: Low work
    1. Low compliance, high elastance
  - Vent Settings: Volume Control
- **Teaching Point: Didactic**
  - Circuit pressure is work required for ventilator to deliver set flow

Volume vs. Pressure Targeted Ventilation Review

- **Teaching Point: ASL 5000 Modeling**
  - ASL Settings: High work
    1. Low compliance, high elastance
  - Vent Settings: Volume Control
- **Teaching Point: Didactic**
  - Circuit pressure decrease reflects elevated patient work

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WOB Under Intense Muscle Loading

Volume vs. Pressure Targeted Ventilation Review

- **Teaching Point: ASL 5000 Modeling**
  - ASL Settings: High work
    1. Low compliance, high elastance
  - Vent Settings: Pressure Control
- **Teaching Point: Didactic**
  - Volume and flow changes

Volume vs. Pressure Targeted Ventilation Review

- **Teaching Point: ASL 5000 Modeling**
  - ASL Settings: Low work
    1. Low compliance, high elastance
  - Vent Settings: Pressure Control
- **Teaching Point: Didactic**
  - Volume and flow changes based off decreased patient work
  - To modify tidal volume, ventilator work needs to be adjusted (↑ or ↓)

Dual Mode Ventilation Review

Adaptive Pressure Control (APC)

- **Teaching Points: Didactic**
  - Underestimating/inappropriate level of support in pressure targeted modes
  - Application and interpretation of Adaptive Pressure Control (APC)
  - Neural drive to preserve minute ventilation, not target pressure
    - APC in low vs. high patient effort
      - Effect on airway pressures (peak inspiratory and mean airway pressures)
        - What does this mean in the setting of lung injury?

Volume vs. Pressure Targeted Ventilation Review

- **Teaching Point: ASL 5000 Modeling**
  - ASL Settings: Low work
    1. Low compliance, high elastance
  - Vent Settings: Adaptive Pressure Control

Volume vs. Pressure Targeted Ventilation Review

- **Teaching Point: ASL 5000 Modeling**
  - ASL Settings: High work
    1. Low compliance, high elastance
  - Vent Settings: Adaptive Pressure Control

Adaptive Pressure Control (APC)

- **Teaching Points: ASL 5000 Modeling**
  - Shifting of ventilator output under loading
  - Phenomena of runaway in actively breathing patients
  - Illusion of “extra” lung protection

WOB Under Intense Muscle Loading

- **Teaching Points: ASL 5000 Modeling**
  - Ventilator WOB decreasing as P_{MUS} increases
    - Decrease in ventilator work output shifts WOB to patient

UCSF
University of California
San Francisco

LUNCH
EXHIBIT HALL OPEN

Friday, January 18, 2019 – 12:05 p.m. – 1:10 p.m.

CONSEQUENCES OF UNINTENDED INTUBATION

Neil MacIntyre, MD
Duke University
Professor of Medicine

Friday, January 18, 2019 – 1:10 p.m. – 1:55 p.m

Presentation has been cancelled due to family illness.

ARDS, RESPIRATORY FAILURE AND BLOOD BIOMARKERS

Angela Rogers, MD
Stanford University
Assistant Professor of Medicine

Friday, January 18, 2019 – 1:55 p.m. – 2:40 p.m.

Angela Rogers, MD, MPH, received her medical degree from Harvard Medical School, and her Masters in public health from the Harvard School of Public Health, and pursued post-graduate training at the Brigham and Women's Hospital and Harvard Combined fellowship. She is an Assistant Professor in Pulmonary and Critical Care Medicine at Stanford University, where her research focuses on using genetics and genomics to identify novel biology in ARDS.

Precision medicine & the role for biomarkers in ARDS

Angela Rogers
Stanford University
California Thoracic Society
January 18, 2019

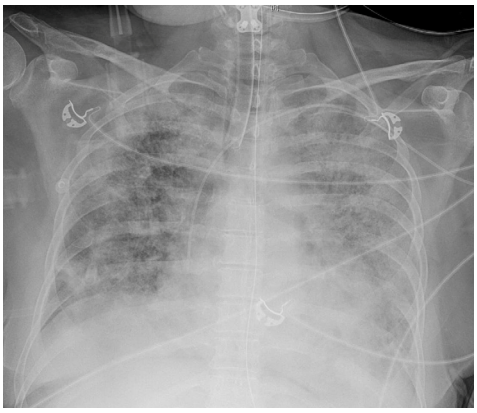
Conflicts of Interest

- I have no conflicts of interest

Learning objectives

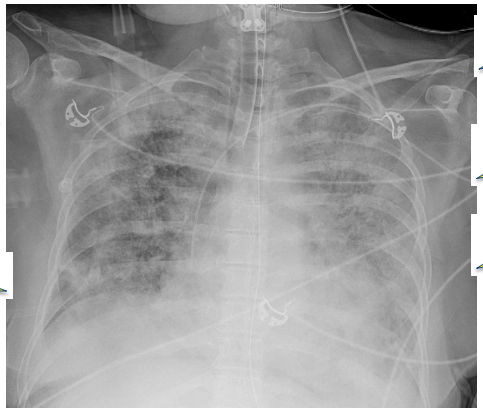
- To understand the need for biomarkers in ARDS
- PaO2:FIO2: A biomarker that works in ARDS
- Biomarkers for endotyping or "splitting" ARDS:
  - Latent class modeling of plasma
  - Molecular phenotyping of edema fluid

ARDS is defined very simply

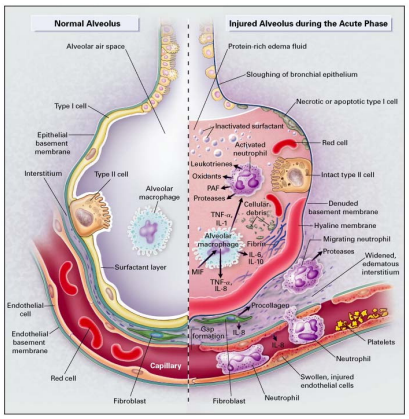


- Intubated
- Acute
- P:F ratio <300
- Bilateral opacities
- Not explained by hydrostatic edema

Diverse underlying risk factors



ARDS pathophysiology is complex

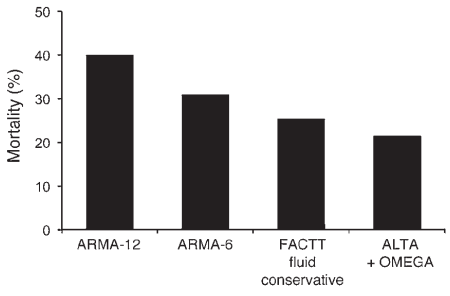


Ware & Matthay, NEJM 2000

"Lumping" vs "Splitting"

What have we learned from lumping?

- ARDS is common
  - 10% of all ICU & 23% of acute respiratory failure admissions
- In real world carries high mortality rate
- Major benefit of low tidal ventilation



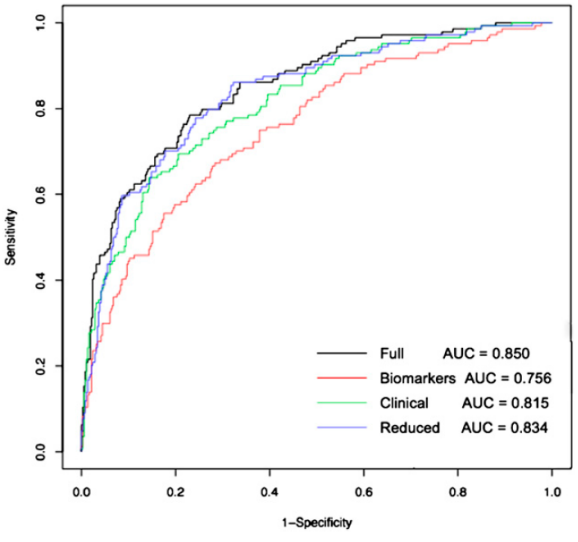
Bellani et al, *JAMA* 2016
ARDSNET *NEJM* 2000
Matthay et al. *JCI* 2012

Biomarkers in all of ARDS

		90-day mortality		
Pathway	**Biomarker**	**Alive**	**Die**	**p-value**
Inflammation	IL-6	209	322	0.004
	IL-8	35	64	<0.001
	TNFR	3668	6914	<0.001
Coagulation & fibrinolysis	Protein C	82	68	.011
	PAI-1	54	111	<0.001
Endothelial injury	ICAM	854	1072	<0.001
	VWF	370	477	<0.001
Epithelial injury	SP-D	92	124	.01

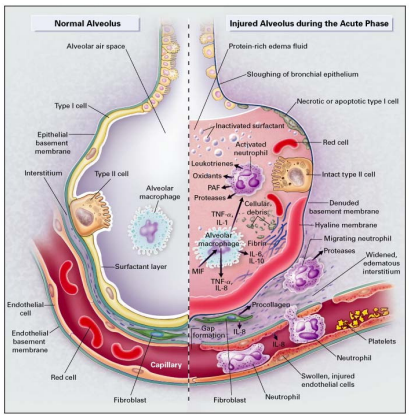
Ware LB, *Chest* 2010

Combining biomarkers to improve prediction based on ALVEOLI trial



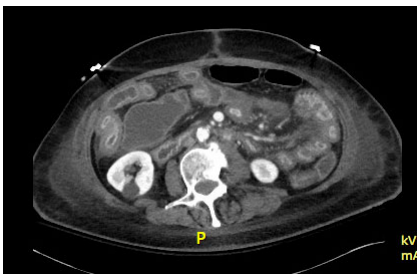
Ware LB, *Chest* 2010

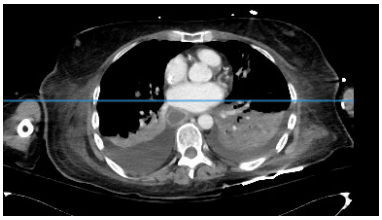
Is it possible that lumping all of ARDS together is harming ARDS clinical trials & science?

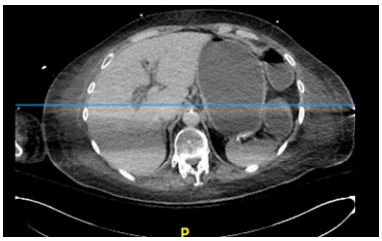


Why splitting matters: a case to classify

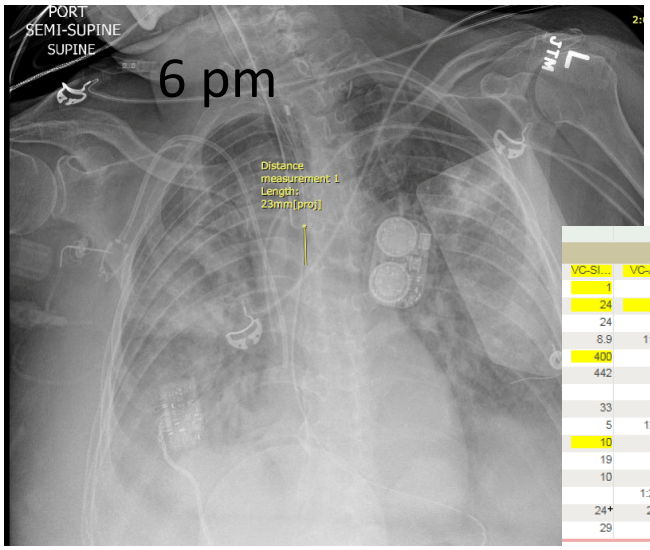
- 70 yo F with colon CA on chemo, recently discharged after 1 week admission for failure to thrive
- Per husband, was nauseated, ”gurgling” all night
- Returns to ED critically ill







10-11	11-12	12-13	13-14	14-15	15-16	16-17	17-18	18-19	
			None			None	None	Nor	
			None			None	None		
36.3 ...	35.8 ...		36 (9...	36.5...+			--≡	-	
24+	24+	24+	24+	26+			26		
95	76	85	80	87	87	83	92	8	
	76/53		105/70	113/72+	57/41	140/79	88/63	90/7	
	63		52	88+	77	105	73	79	
107/61	87/68	74/50	101/72	120/71+					
	67		54						
		80 kg...				79.4 ...			
	89		86	82	88	85		83	
								83	
38									
				1 mg/...		1 mg/...	1 mg/...	1 mg/	amiodarone Do...
			0.1 ...+	0.03...+	0.3 m...	0.24...+	0.2 ...+	0 mc...	epinephrine Do...
					0.5 m...	1 mg...+	1 mg/hr≡	1 mg/l	hydromorphone...
					1 mg/hr	2 mg...+	2 mg/hr≡	2 mg/l	midazolam Dos...
5 mc...+	15 m...+	20 mc...	20 m...+			20 mc...	20 mc...	20 m...	norepinephrine...
					100 m...	100 m...	100 m...	100 m	phenylephrine...
			*1 U...+			0.04 ...	0.04 ...	0.04	vasopressin Do...
			VC-SI...	VC-AC		VC-AC			
			1			1			



VC-SI...	VC-AC		VC-AC
1			1
24	28	32	32
24			32
8.9	11.2	11.2	10.8
400		350	350
442			
			0
33	35	36	37
5	12	16	18
10			
19	27	28	33
10			24
	1:2.3	1:2.1	1:2.1
24+	23+	27+	22
29			21

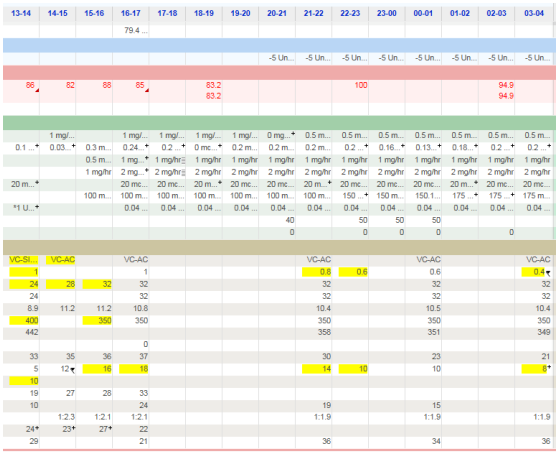
ARDS clinical trial enrollment

	Live	Die
Paralytic		
Placebo		

ARDS biobank

	ARDS	Not ARDS
Patient #1		

Overnight respiratory improvement



- 6 pm: FIO2 1.0, PEEP 18, Pplat 37, ABG 7.23/60/55
- 3 am: FIO2 0.4, PEEP 8, Pplat 21, ABG 7.23/60/90
- 9 am: MAP falls to 40, pH 6.8/55/80, c/w bowel perforation

What does this case do to our clinical trial and biobank?

	Live	Die
Paralytic		
Placebo		

	ARDS	Not ARDS
Patient #1		

Misclassification in ARDS really matters for clinical trials

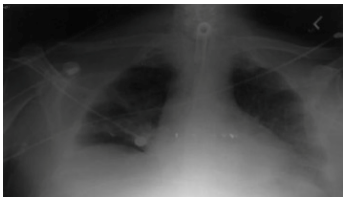
- Inter-rater CXR interpretation varies from κ ~.4-.9

K = 1

	ARDS	Not ARDS
ARDS	50	
Not		50

K = .6

	ARDS	Not ARDS
ARDS	40	10
Not	10	40



K = .4

	ARDS	Not ARDS
ARDS	40	20
Not	10	30

Rubenfeld et al. *Chest* 1999

Power for clinical trials dramatically falls with misclassification

RCT power estimate when ARDS enrollment is imperfect from a patient cohort with 25% ARDS prevalence

Inter-observer Agreement	Kappa	Power in 1500 patient trial	Sample size for 90% power
Perfect	1.00	0.92	1402
Almost perfect	0.85	0.87	1664
Substantial	0.72	0.81	1968
	0.61	0.74	2320
Moderate	0.51	0.67	2726
	0.42	0.60	3198

Sjoder et al. *Annals ATS* 2016

A major role for biomarkers may be in "Splitting" ARDS

- Prognostic: Identify patients at highest risk of bad outcomes and death
- Predictive: Identify patients who would benefit most from treatment

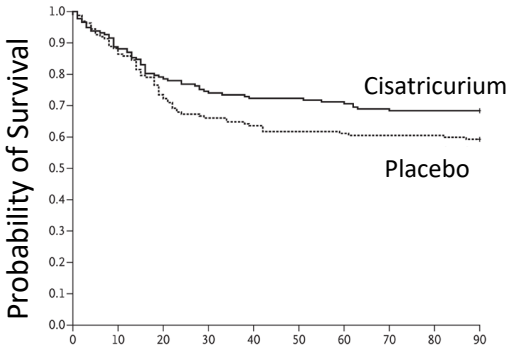
PaO2:FIO2 ratio as a critical ARDS biomarker

- PaO2:FIO2
  - P:F ratio defines disease severity
    - Prognostic, outperforms other, more complex models
  - Enriches clinical trials: recruiting based on more stringent thresholds
    - Predictive enrichment

AECC consensus conf, *AJRCCM* 1994
Berlin definition, *JAMA* 2014

P:F <150 → positive clinical trials

Neuromuscular blockade

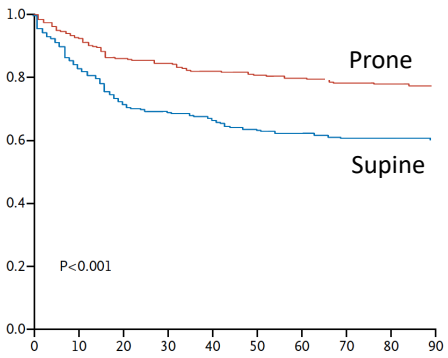


Lower hazard for death (.68, p=.04)

31.6% vs 40.7% 90-day mortality (p=.08)

NEJM. 2010, 373: 1107-16

Prone positioning

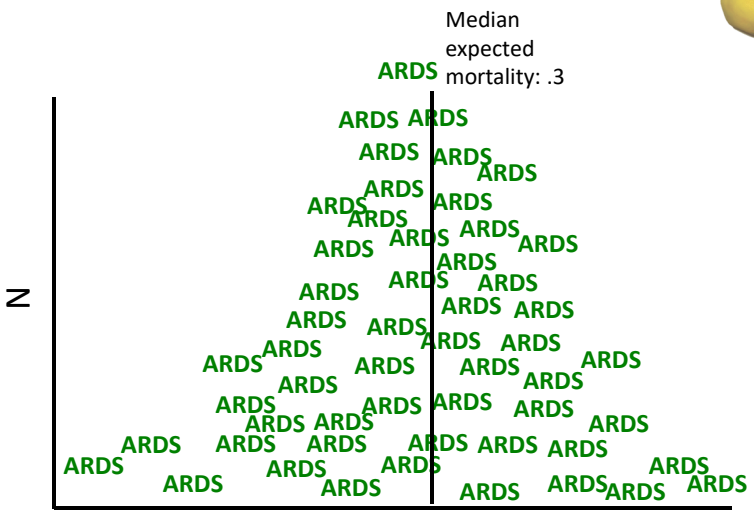


16% vs 32.8% 28d mortality (p<.001)

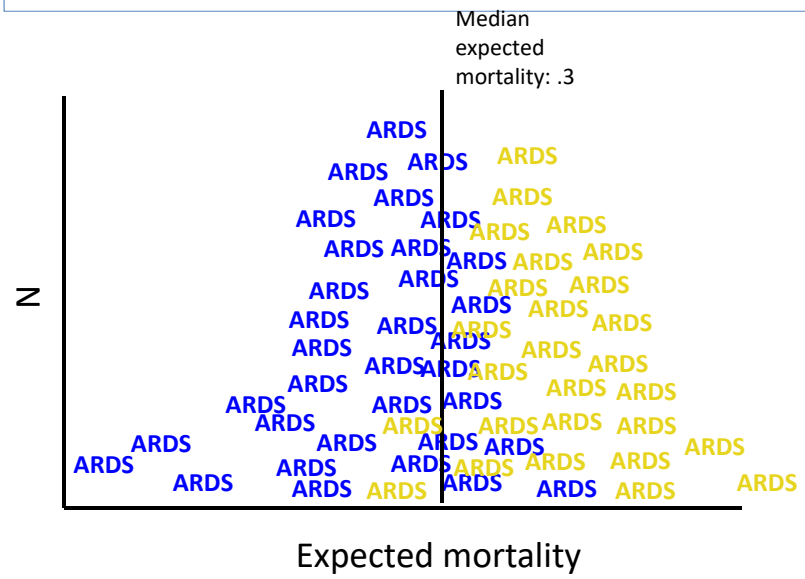
23.6 vs 41% 90d mortality (p<.001)

NEJM. 2013, 368: 2159-67

Biomarkers for splitting



Biomarkers for splitting



2 examples

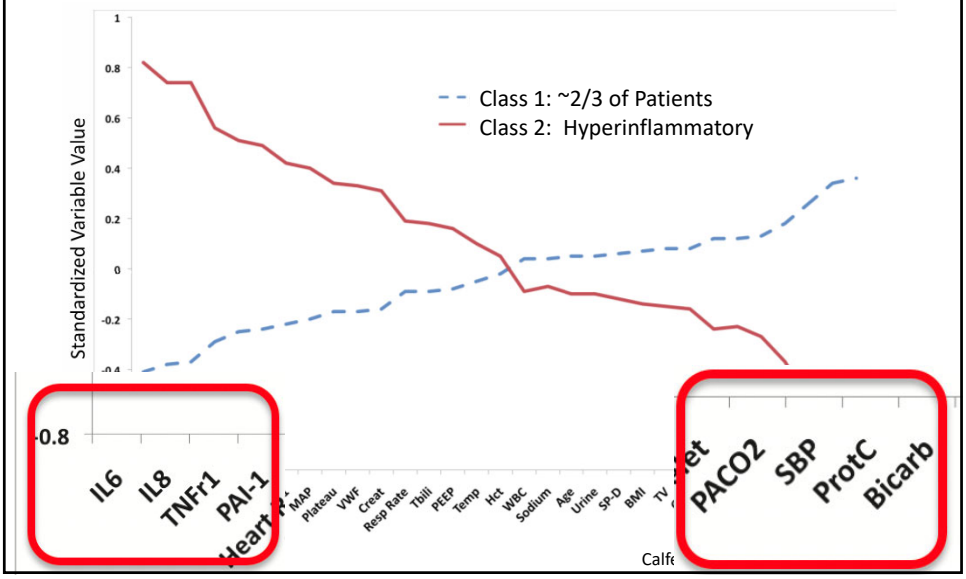
- Latent class modeling, identified plasma biomarkers
- Metabolomics of pulmonary edema fluid

Latent Class Analysis: Are There Distinct Subtypes of ARDS?

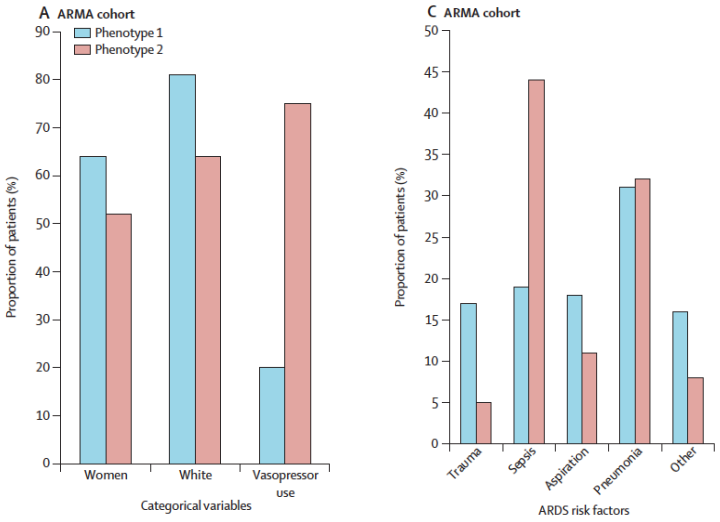
- Study population: Three ARDSnet clinical trials
  - First cohort: ARMA (low tidal volume only; n=479)
  - Second cohort: ALVEOLI (low vs. high PEEP; n=549)
  - Third cohort: FACCT (conservative vs liberal fluid; n=1000)
- Clinical and biomarker data from baseline in each study as inputs that "identify" class (endotype)
  - Analysis conducted independently in each cohort
  - Outcomes not considered in class modeling

Calfee CS et al, *Lancet Resp Med* 2014
Famous K et al, *AJRCCM* 2016

What variables are important in class definition?



Classes differ by clinical variables



Calfee CS et al, *Lancet Resp Med* 2014

Mortality differs by class

	90-day mortality		
Study	**Class 1 (~2/3) ARDS**	**Class 2 (~1/3) ARDS**	**p-value**
ARMA	23%	44%	0.006
ALVEOLI	19%	51%	<0.001
FACTT	22%	45%	<0.0001

Class could be defined w/ >90% AUC with 3 factors: IL8, TNFr1, bicarbonate

Calfee CS et al, *Lancet Resp Med* 2014
Famous K et al, *AJRCCM* 2016

Response to Therapy differs by class

ALVEOLI ($p_{interaction}$=.049)

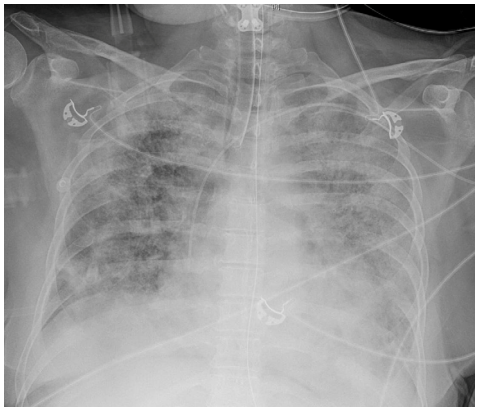
	Mortality in Class 1 ARDS (n=404)	Mortality in Class 2 ARDS (n=145)
Low PEEP	16%	51%
High PEEP	24%	40%

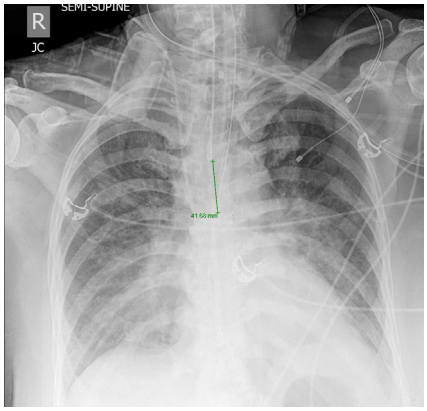
FACCT ($p_{interaction}$=.004)

	Mortality in Class 1 ARDS (n=727)	Mortality in Class 2 ARDS (n=273)
Liberal fluid	18%	50%
Conservative fluid	26%	40%

Calfee CS et al, *Lancet Resp Med* 2014
Famous K et al, *AJRCCM* 2016

Metabolomics of pulmonary edema fluid: ARDS vs CHF





Pulmonary edema fluid metabolomics

- Undiluted pulmonary edema fluid in ARDS
  - High edema: plasma protein ratio (>.65) associated with ARDS (AUC >.8)
- Pulmonary edema fluid at time of intubation
  - 16 ARDS vs 13 CHF
  - Collected at Vanderbilt and UCSF

Rogers et al. *AJP Lung* 2017

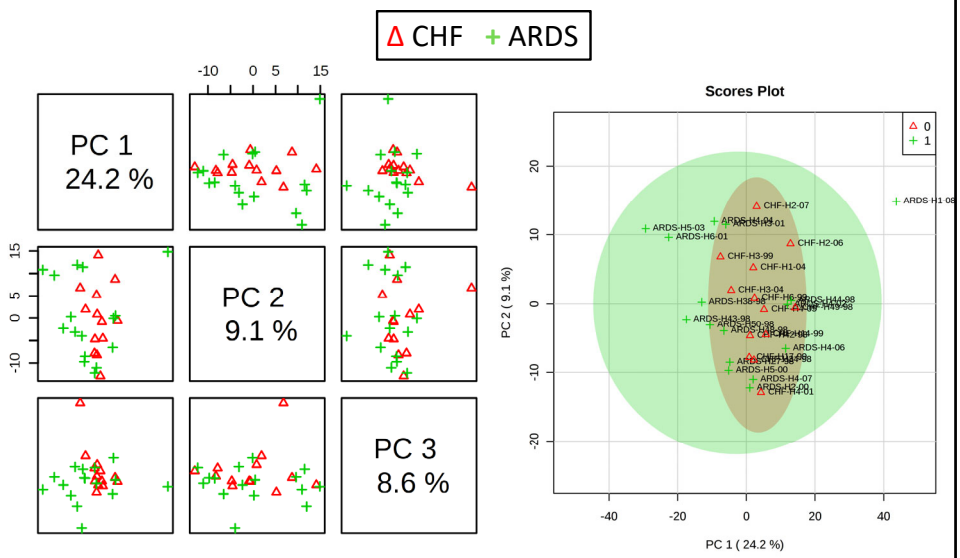
CHF vs ARDS Phenotyping

	ARDS (N=16)	CHF (N=13)	P value
Age	43.7	50.5	.3
Gender (%M)	50%	62%	.7
Sepsis	44%	0%	.008
Mortality	44%	15%	.12
Primary Diagnosis	Pneumonia (4) Sepsis (4) Anaphylaxis (2) Aspiration (1) TRALI (2) Fulm Hep Fail (1) Reperfusion edema (1) Tumor lysis (1)	Vol overload/CHF (5) MI/Ischemia (2) Cardiac arrest (1) Post-obstructive (2) Cardiogenic shock (1) TRALI (1) Neurogenic (1)	.01

Metabolic profiling strategy

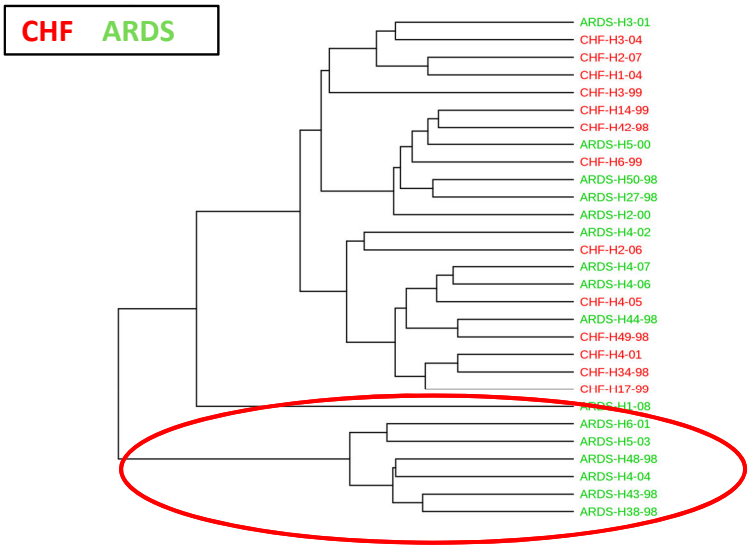
- Undiluted pulmonary edema fluid profiled by Metabolon
- Tests up to 3000 human plasma metabolites with high accuracy
- Metabolite levels $\log_2$ normalized and auto scaled
- Differences in classes assessed using machine learning
  - Principle components analysis
  - Partial least squares-discriminant analysis
  - Hierarchical clustering

No separation of CHF vs ARDS



Rogers et al. *AJP Lung* 2017

Hierarchical clustering: A subset separates



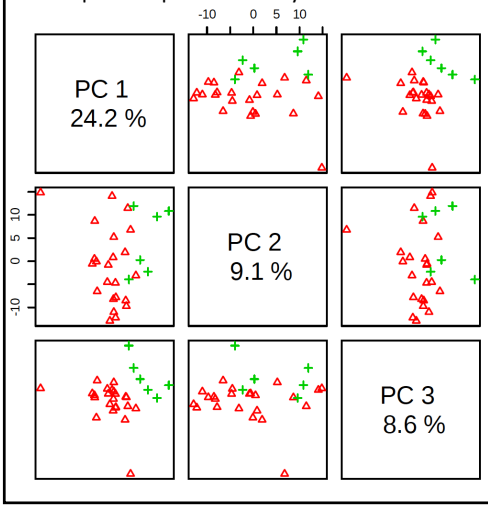
6 Separate ARDS

	6 Distinct ARDS	10 Remaining ARDS	CHF
Age	36	49	51
Gender (%M)	33	60%	62%
Sepsis	66%	30%	0%
Mortality	66%	30%	15%
Primary Diagnosis	Sepsis (3) Fulm Hep Fail (1) Anaphylaxis (1) Aspiration (1)	Pneumonia (4) Sepsis (1) Anaphylaxis (1) TRALI (2) Reperfusion edema (1) Tumor lysis (1)	Vol overload/CHF (5) MI/Ischemia (2) Cardiac arrest (1) Post-obstructive (2) Cardiogenic shock (1) TRALI (1) Neurogenic (1)

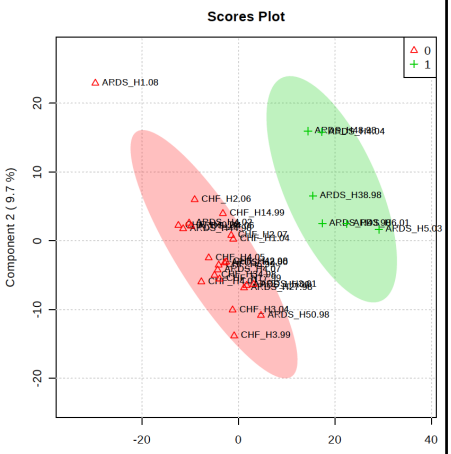
These 6 separate

Δ CHF & 10 ARDS + 6 distinct ARDS

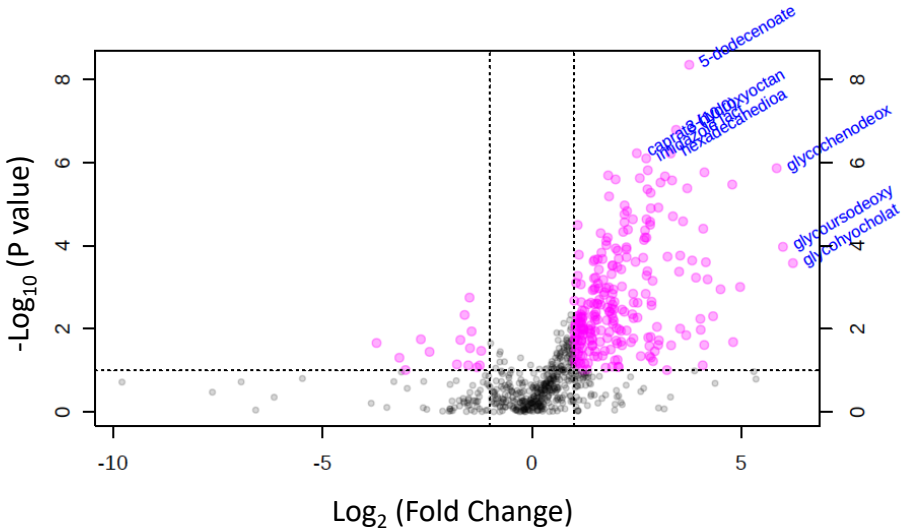
Principal Components Analysis



Partial Least Squares DA

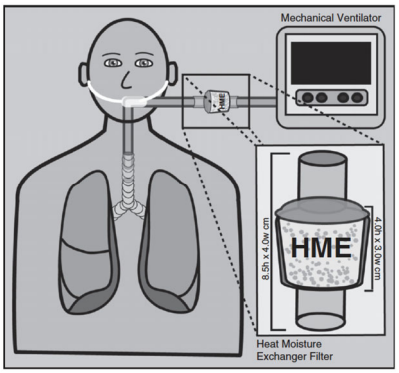


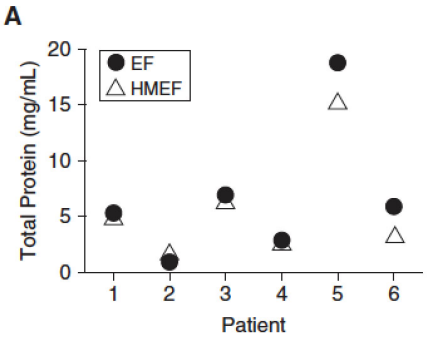
These 6 are highly metabolically active



Rogers et al. *AJP Lung* 2017

Pulmonary edema: A newly attainable biomarker?





McNeil et al. *AJRCCM* 2018

Should we be lumping or splitting ARDS?

Should we be lumping AND splitting ARDS?

Should we be lumping AND splitting ARDS?

Low tidal volume, lung protective ventilation

- Clearly helps mortality in ARDS
- Little downside in some misclassification

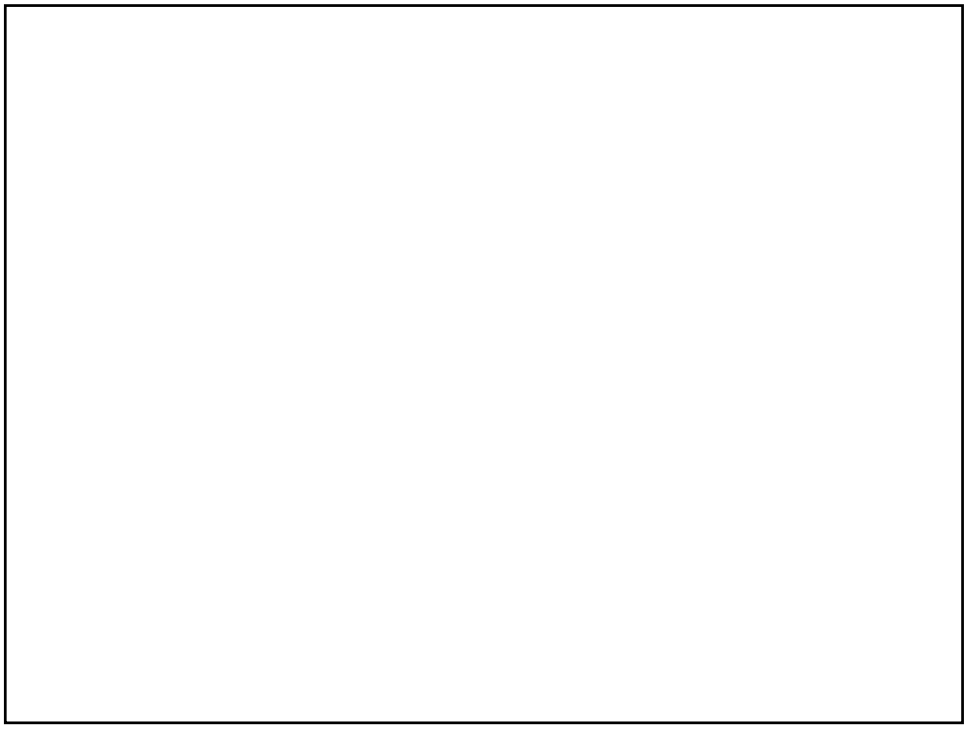
Should we be lumping AND splitting ARDS?

ARDS clinical trials

- Genomics tells us we need to be careful with lumping
  - Endotypes
  - Frank misclassification
- Kills power of trial & puts patients who can't benefit at risk

Conclusions

- Lumping all of ARDS as a single phenotype has been very successful for lung protective ventilation and reduced mortality
- For moving toward precision medicine:
  - To date our only established biomarker in ARDS is the P:F ratio, which is prognostic and predictive
  - Biomarkers will likely be critical in endotyping ARDS & moving toward personalized medicine in practice and clinical trials



BREAK
EXHIBIT HALL OPEN

Friday, January 18, 2019 – 2:40 p.m. –3:00 p.m.

NEW STRATEGIES IN AEROSOLIZED THERAPIES IN CRITCAL CARE

Jim Fink, PhD, RRT, FAARC, FCCP
Aerogen Pharmaceuticals
Chief Scientific Officer

Friday, January 18, 2019 –3:00 p.m. – 3:45 p.m.

Jim Fink, PhD, RRT, FAARC, FCCP, Currently serves as Chief Scientific Officer for Aerogen Pharma Corp in San Mateo, CA. Dr. Fink is an Adjunct Professor of Respiratory Therapy at Rush Medical School, Chicago, and Visiting Professor, Department of Physical therapy, Universidade Federal de Pernambuco, Recife, Pernambuco, Brazil (CNPq 400801/2013-2). A respiratory care clinician, supervisor, manager, educator and researcher for 45+ years with focus on understanding aerosol device/patient interface and design in both critical care and ambulatory settings.

New Strategies in Aerosolized Therapy in Critical Care

Jim Fink, RRT, PhD, FAARC, FCCP
Chief Science Officer, Aerogen Pharma Corp., San Mateo, CA USA
Visiting Professor, Universidade Federal de Pernambuco, Brazil
Adjunct Faculty, Rush, Chicago

CALIFORNIA THORACIC SOCIETY
NORTHERN CALIFORNIA
ANNUAL EDUCATIONAL CONFERENCE
FRIDAY JANUARY 18, 2019 -
SATURDAY JANUARY 19, 2019

What do we know?

- **In vitro data showing that different types of nebulizers perform differently (JN, USN, VM, etc.)[4,5,6]**
- **In vitro data demonstrating best placement for optimal aerosol delivery with different applications (MV, NIV, HFNC)[4,5,6,7,8]**
- **In vitro data with different interfaces[8]**
- **Imaging data with different applications comparing different nebulizers[9, 10, 11, 12, 14]**
- **Recent advances in aerosol generators have led to more efficient aerosol delivery**

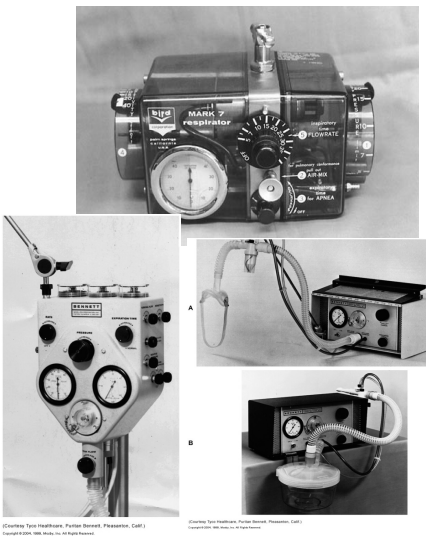
Gaps

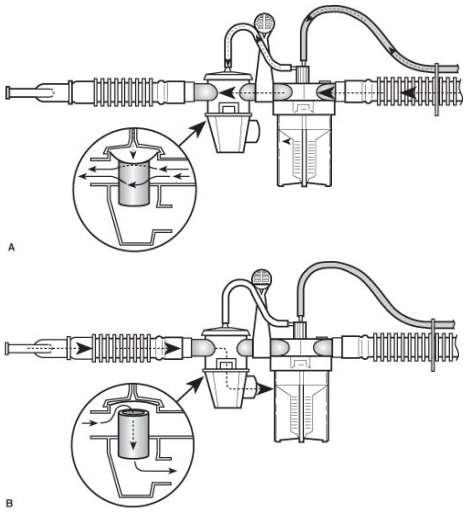
- **No aerosol drugs approved for use in critical ill adults**
  - Approvals based on ambulatory studies in patients with mild disease
- **Aerosol delivery with JN is less efficient in critical care applications[1]**
- **Numerous factors effect performance[2]**
- **Lung deposition is a relatively low fraction of total aerosol dose.[3]**
- **Aerosol delivery with mechanical ventilation is limited and technique dependent[2]**
- **Newer applications such as HFNC require recommendations for aerosol delivery**
- **Wide range and variance in efficiency between different types of nebulizers across applications**
- **Little clinical data exists to support optimal aerosol delivery recommendations in critical care**

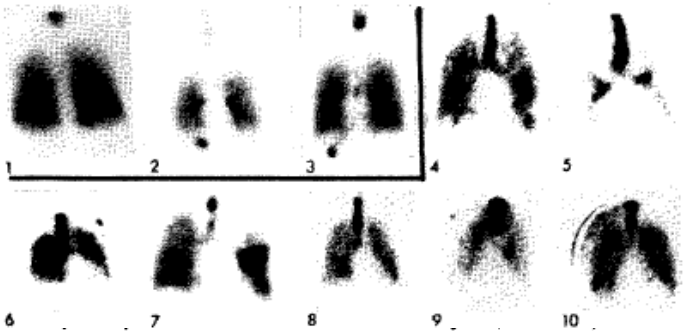
Medications via Aerosol to Acutely Ill Patients

- **Bronchodilators**
- **Anti-infectives**
- **Prostanoids**
- **Anticoagulants - Heparin**
- **Diuretics**
- **Insulin**
- **Mucokinetics**
- **NOTE: Mucomyst (N-Acetylcystein) – no evidence of benefit by aerosol on or off the ventilator**

Intermittent Positive Pressure Breathing (IPPB) – 30% Less Aerosol to lung than Neb Alone

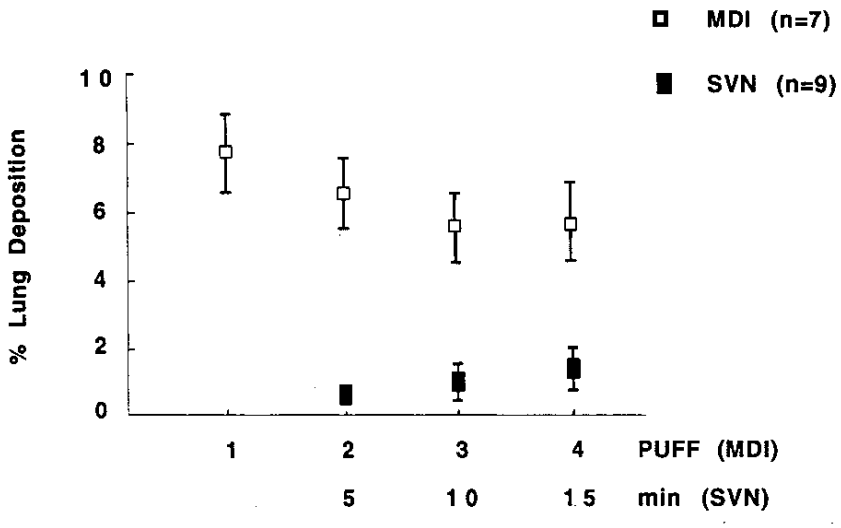






	Intubated Subjects	Nonintubated Subjects
Administered radioactivity	5.75 ± 1.3 mCi	6.53 ± 0.4 mCi
Percent of administered radioactivity in:		
Trachea (includes portion of endotracheal tube in intubated patients)	1.6 ± 1.1%[a]	0.3 ± 0.1%[a]
Lung parenchyma	2.9 ± 0.7%[b]	11.9 ± 2.2%[b]
Stomach	—	7.3 ± 2.05%
Oral cavity	—	15.0 ± 13%
Nebulizer circuitry	—	65.5 ± 16%

Macintyre Crit Cre Med 1985

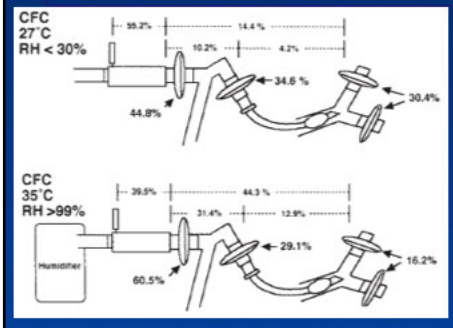


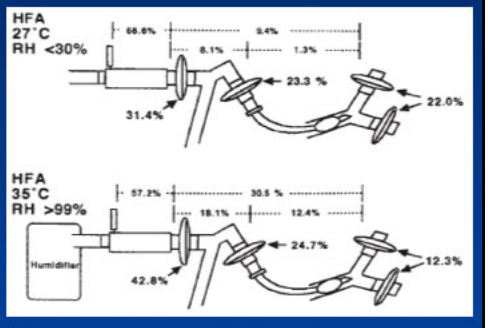
Fuller et al. 1990. ARRD 141:440-444.

Drug deposition

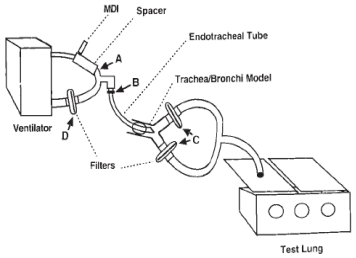
CFC formulated albuterol

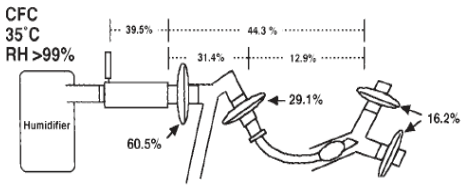
HFA formulated albuterol





Fink et al. AJRCCM 1999: 159; 63-67





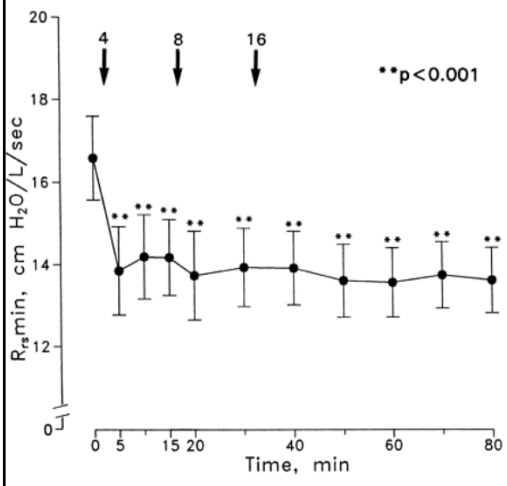
IN VIVO AND *IN VITRO* ESTIMATES OF EXHALED ALBUTEROL DURING CONTROLLED MECHANICAL VENTILATION

Patient No.	Sex	ETT (*mm*)	V_T (*L*)	Rate (*b/min*)	PIF (*L/min*)	Ti/Ttot	Albuterol on Expiratory Filter*		
							In Vivo	*In Vitro*	Difference†
1	M	8.0	0.7	12.0	40	0.21	9.6	4.4	5.2
2	M	8.0	0.7	10.0	40	0.18	8.7	3.9	4.8
3	M	8.5	0.6	10.0	40	0.15	9.3	4.1	5.2
4	F	7.5	0.6	12.0	40	0.18	8.6	4.1	4.5
5	M	8.0	0.7	10.0	40	0.18	6.2	3.3	2.9
6	F	7.0	0.5	12.0	40	0.15	8.7	3.9	4.7
7	M	8.0	0.6	10.0	40	0.15	9.0	3.9	5.1
8	M	8.0	0.6	12.0	50	0.14	7.9	3.6	4.3
9	M	8.0	0.7	10.0	40	0.18	10.8	4.6	6.2
10	M	8.0	0.6	12.0	40	0.17	8.7	3.6	5.1
Mean		7.9	0.6	11.0	41	0.17	8.7	3.9	4.8
SD		0.4	0.1	1.1	3.2	0.02	1.2	0.4	0.8

Definition of abbreviations: ETT = endotracheal tube diameter; PIF = peak inspiratory flow; Ti/Ttot = duty cycle; V_T = tidal volume.
* Expressed as percent of nominal dose.
† The difference between *in vivo* and *in vitro* values, at similar settings of controlled mechanical ventilaton, is the estimate of the amount of aerosol exhaled by the patient.

AM J RESPIR CRIT CARE MED 1999;159:63–68.

Clinical response to pMDI during CMV

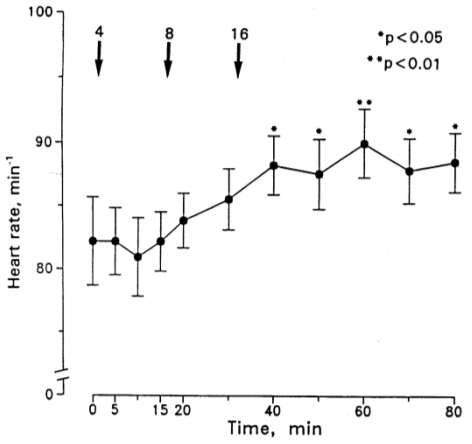


- Dose response in mechanically ventilated patients with COPD.
- MDI-spacer & albuterol
- Similar decline in airway resistance with 4, 8 and 16 puffs of albuterol.

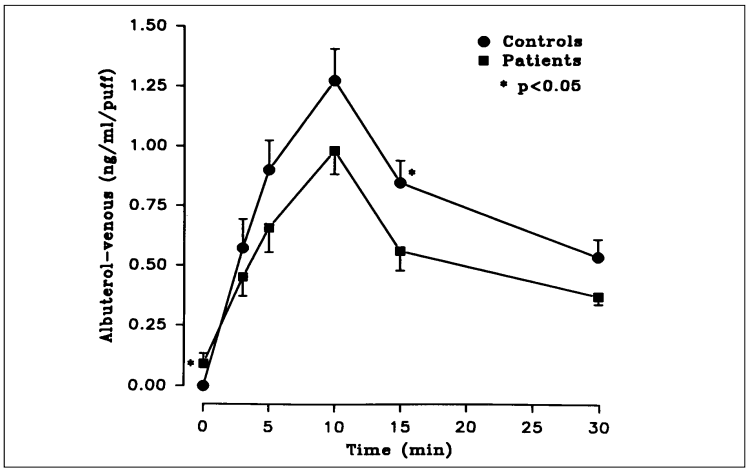
Dhand R AJRCCM 154;388:1996

Toxicity

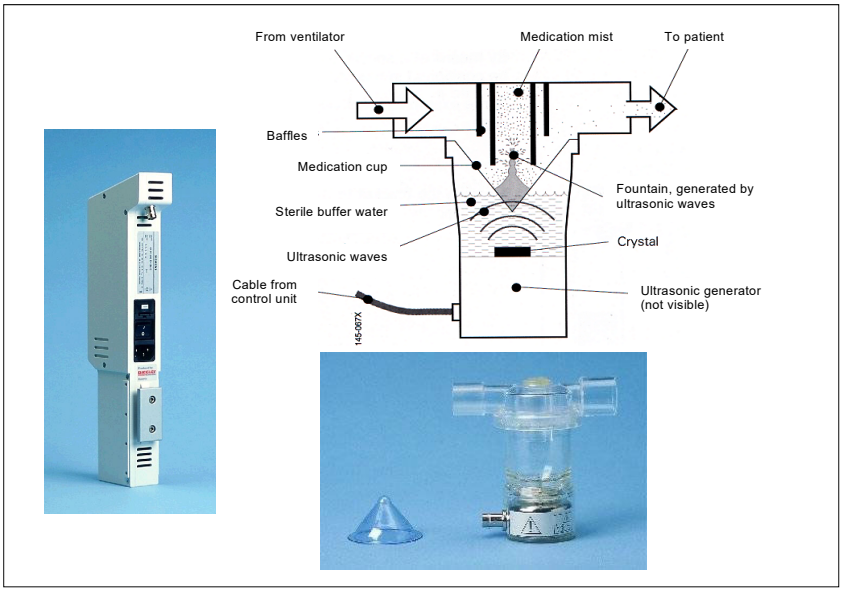
- **Increase in heart rate after 28 puffs of MDI albuterol.**
  AJRCCM 1996;154:388
- **Ventricular ectopy and SVT developed after 3-6 times normal nebulizer dose.**
  Am Rev Resp Dis 1993;148



Comparison of Serum Albuterol Levels: Normal Controls and Intubated/Ventilated Subjects

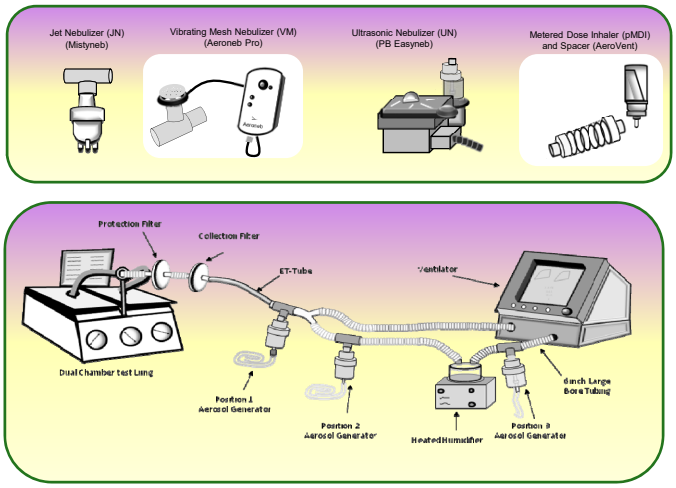


Duarte et al. 1996, AJRCCM

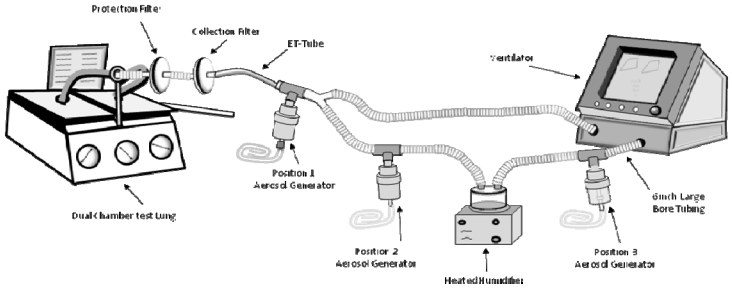


Maquet SUN 145 Ultrasonic Nebulizer with power control module.

Four types of aerosol generators in 3 positions during CMV with no bias flow

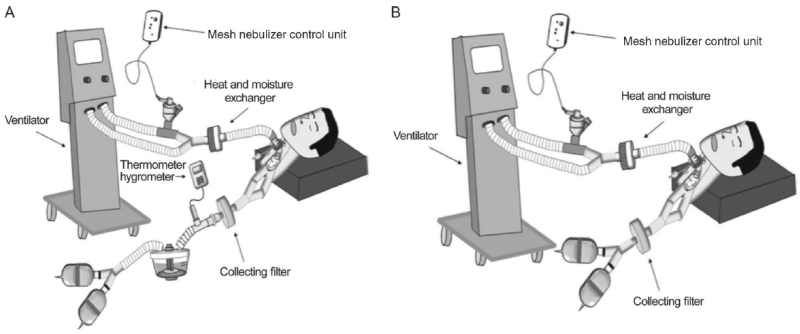


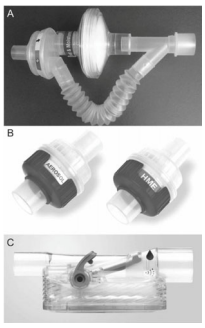
Ari et al. Respiratory Care 2010; 55 (7): 837-844.



Neb Position	Pos 1 - Between ETT & Y		Pos 2 - 6 in from Y		Pos 3 - 6 in from Vent	
Ventilator Circuit	Heated	Unheated	Heated	Unheated	Heated	Unheated
JN	**4.66 (0.5)**	**7.62 (0.9)**	**3.61 (0.2)**	**9.66 (1.5)**	**5.98 (0.1)**	**14.66 (1.5)**
VM	**12.82 (0.5)**	**14.54 (1.0)**	**16.79 (2.6)**	**30.24 (1.0)**	**8.39 (2.1)**	**24.20 (1.2)**
UN	**10.07 (3.9)**	**10.70 (1.5)**	**16.53 (4.3)**	**24.68 (4.4)**	**4.59 (2.0)**	**10.51 (0.3)**
pMDI	**7.6 (1.3)**	**22.1 (1.5)**	**17 (1.0)**	**27.8 (3.3)**	**2.5 (0.8)**	**7.9 (1.5)**

Ari et al, Respir Care 2010



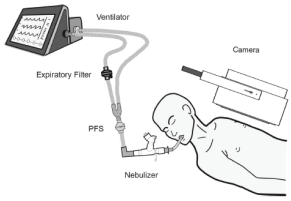


Exhaled Humidity	Dose Delivered (%)			
	Control	AirLife	CircuVent	Humid-Flo
With	10.8 ± 0.2	9.2 ± 0.7	9.8 ± 1.9	9.9 ± 1.1
Without	18.0 ± 0.7	12.0 ± 0.5	12.6 ± 0.8	15.3 ± 0.8

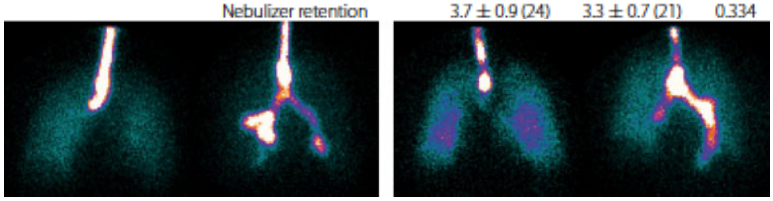
Results are mean ± SD.

Ari et al, Respir Care 2017

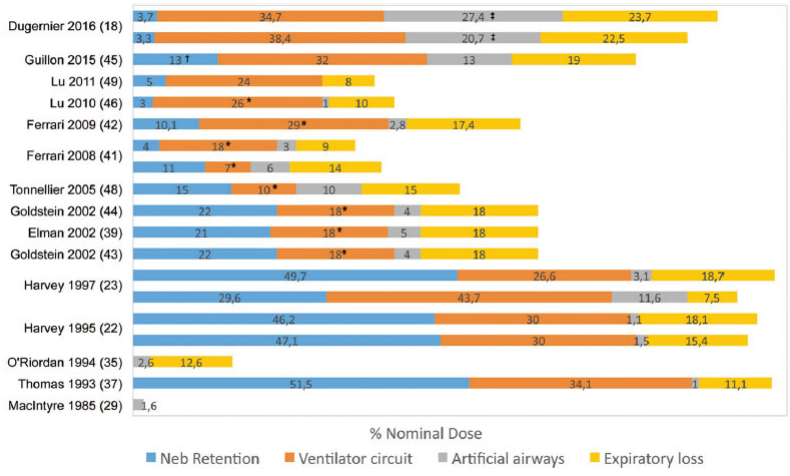
Aerosol Delivery During PSV and VCV

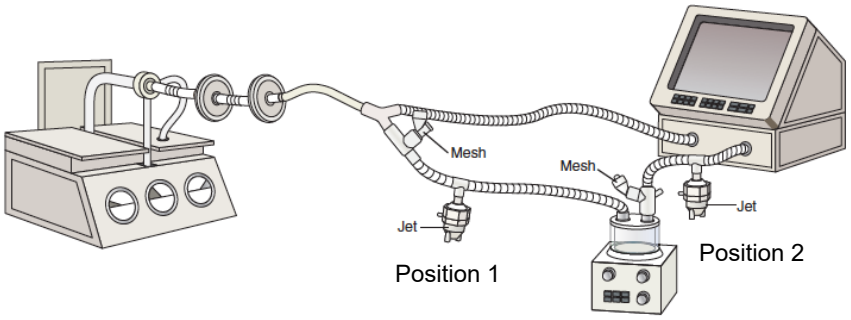


	PSV ($n = 8$)	VCV ($n = 9$)	p value
Pulmonary deposition (%)	*10.5 ± 3.0 (28)*	*15.1 ± 5.0 (33)*	*0.038*
Right lung	6.1 ± 1.9 (31)	10.6 ± 5.8 (55)	0.057
Penetration index	0.75 (0.30–0.94)	0.32 (0.16–0.77)	0.210
Left lung	4.1 (3.8–4.6)	4.5 (2.2–5.6)	0.885
Penetration index	0.67 (0.53–0.86)	0.74 (0.6–1.06)	0.211
Right/left lung ratio	1.39 (0.91–2.05)	3.33 (0.7–5.38)	0.336
Extrapulmonary deposition (%)	*89.5 ± 3.0*	*84.9 ± 5.0*	*0.038*
ETT and tracheal area	27.4 ± 6.6 (24)	20.7 ± 6.0 (29)	*0.043*
Expiratory filter	23.7 ± 5.3 (22)	22.5 ± 7.6 (34)	0.710
Ventilator circuit	34.7 ± 8.7 (25)	38.4 ± 12.3 (32)	0.486
Proximal pieces	32.0 ± 7.4 (23)	35.9 ± 12.5 (35)	0.451
Insp–expi tubing	2.7 ± 1.9 (70)	2.5 ± 1.7 (68)	0.833
Nebulizer retention	3.7 ± 0.9 (24)	3.3 ± 0.7 (21)	0.334



Dugernier Ann Critical Care 2016





	ADULT STUDY	PEDIATRIC STUDY
Mode	Volume Control	Volume Control
Tidal Volume	500 ml	100 ml
Respiratory Rate	20/min	20/min
PEEP	5 cmH_2O	5 cmH_20
Waveform	Descending	Descending
Bias Flow	2 and 5 lpm	2 and 5 lpm

Ari et al. Respiratory Care 2010; 55 (7): 845-851.

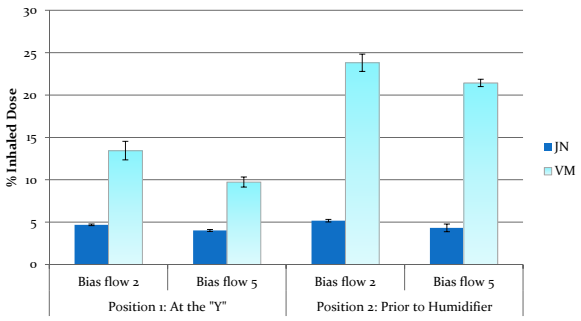
With Bias Flow

VM and JN more Efficient Placed Prior to Humidifier

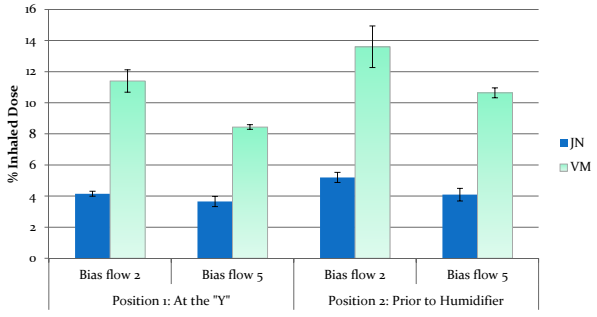
As Bias flow Increases deposition decreases

VM > JN

Adult



Peds



Ari et al. Respiratory Care 2010; 55 (7): 845-851.

Is Nebulization with Inspiration Best?

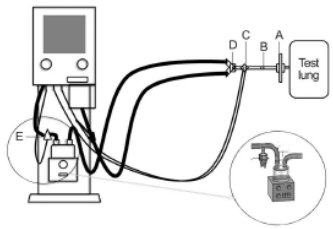
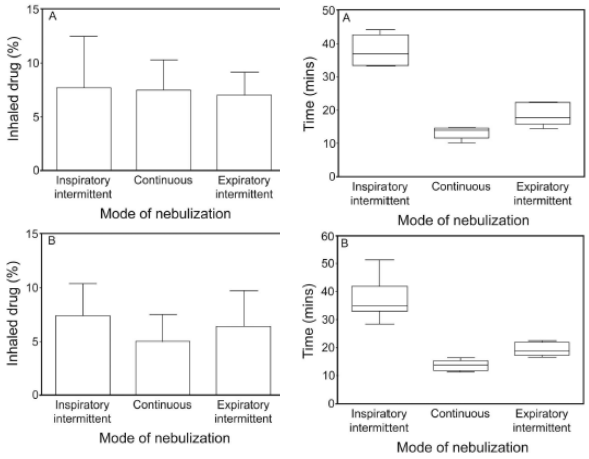


Fig. 1. Diagram of experimental apparatus. A jet nebulizer (E) powered by the ventilator nebulization function was placed in the ventilator outlet 15 cm from the heater, and a filter for aerosol collection (A) was placed distal to the endotracheal tube (B). Also shown are the flow sensor (C) and the Y-piece (D).



Wan et al, Respir Care 2014

Evaluation of aerosol delivery through high frequency oscillatory ventilation

Hui-Ling Lin MSc RRT RN FAARC- Department of Respiratory Therapy, Chang Gung University
Shu-Hua Chiu BS RRT, Tien-Pei Fang MS RRT- Department of Respiratory Therapy, Chiayi Chang Gung Hospital

Background:
High frequency oscillatory ventilation (HFOV) is used with critically ill patients with failed oxygenation on respiratory distress syndrome or acute respiratory distress syndrome as a rescue therapy. However, the efficiency of aerosol delivery during HFOV has not been tested extensively with different devices.

Objective:
The purpose of this *in vitro* study was to determine aerosol delivery by various devices on HFOV with adult, pediatric, and neonate lung models.

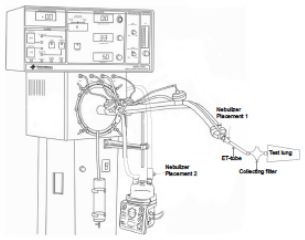
Ventilator settings

Parameter	Neonate	Pediatric	Adult
MAP (cm H_2O)	10	18	30
Bias flow (L/min)	10	25	40
Frequency (Hz)	15	8	5
Inspiratory Time (%)	33	33	33
Power (cm H_2O)	3	7	8

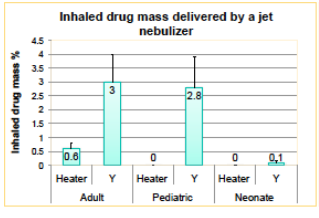
Conclusion:
Aerosol delivery with a vibrating mesh nebulizer placed between the ETT and the ventilator circuit was more efficient than a jet nebulizer during high frequency oscillatory ventilation with infant, pediatric and adult settings.

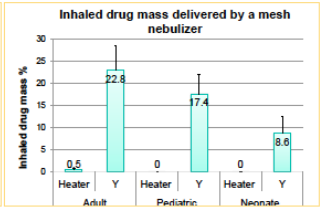
•There is no conflict of interest.

Methods:

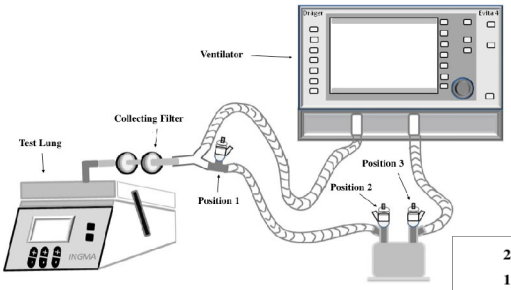


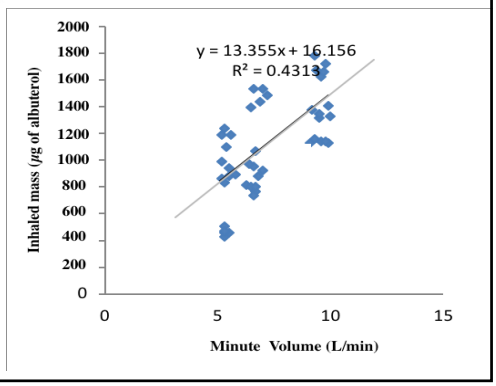
Results: Figures below show Inhaled drug mass ± SD (%) among breathing patterns and locations between two devices.





Aerosol Delivery with APRV





Hui-Qing Ge 2018

Aerosol Delivery with APRV

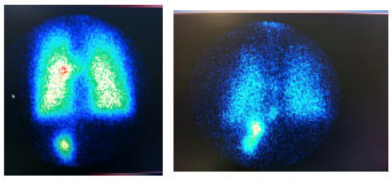
	μg of albuterol (mean ± SD) and percentage of nominal dose		
	Position 1 Insp limb at Y	Position 2 Humidifier outlet	Position 3 Humidifier inlet
PCV	796.9±13.9 (15.9%)	971.9 ± 69.4 (19.4%)	1490.6 ± 61.1 (29.8%)[a]
PCV_{BF6}	1046.88±27.1 (20.8%)[b]	1057.3 ± 52.9 (21.1%)	1182.3 ± 61.4 (23.6%)[ab]
APRV	475.0±28.4 (9.5%)	893.8± 40.4 (17.9%)	1153.1± 99.7 (23.1%)[ab]
APRVs	1153.1±13.1 [d] (23.1%)	1368.8±37.6 (27.4%)	1706.2±60.9 (34.1%)[ac]

Hui-Qing Ge 2018

VMN with Adapter vs Jet Neb

VMN JN

Figure 1. Visual representation of the circuit



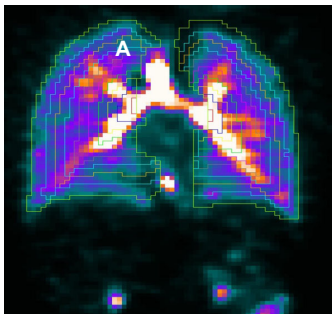
VMN JN

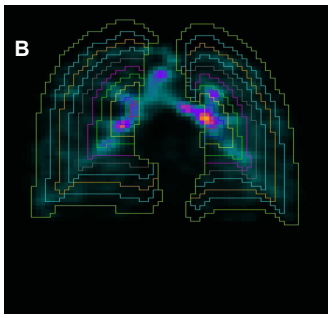
	Jet Neb	VMN/Ultra	p-value
Lung	4.5±1.35	22.8±9.83	0.004
Upper airways	1.7±0.51	3.3±2.08	NS
Stomach	0.9±0.38	3.7±2.18	0.010
Device	13.1±4.60	36.7±15.12	0.037
Nebulizer	75.0±4.46	10.4±9.93	0.004
Expiratory filter	41.4±14.18	18.2±23.22	NS

Alcofocado ATS2016

Mouthpiece Aerosol Delivery

6 Healthy Adults Vibrating Mesh with adapter vs Jet Neb



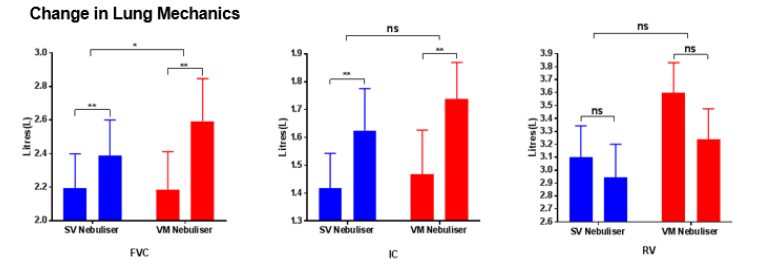


Vibrating Mesh	Jet neb	P value
34.1 ± 6	5.2 ± 1.1	<0.001

- Lung deposition was six times greater with Vibrating Mesh (Aerogen® Ultra) vs the Jet Neb

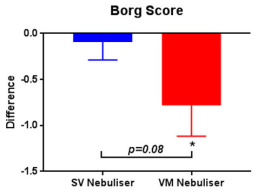
26 11. Dugernier *et al.*

COPD Clinical Outcome Data



Beaumont Hospital COPD Study (VM vs JN)

- VM (Aerogen Ultra) group achieved a significantly greater improvement in post-bronchodilator FVC compared to the Jet Neb group
- Only the VM group demonstrated significant reductions in post-bronchodilator BORG breathlessness score.

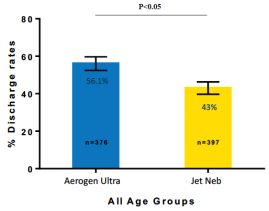


22. Cushen, V., et al.

VMN with Adapter vs Jet Neb in the Emergency Department

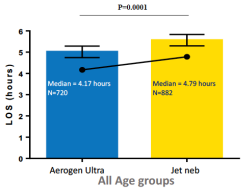
Discharge rates

When compared to the Jet neb group, discharges are 30% higher with Aerogen Ultra



Length of Stay Reduced by 13%

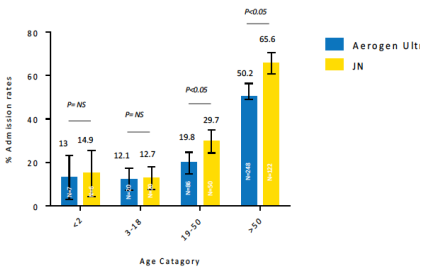
37 minute median reduction in LOS per patient with the Aerogen Ultra v jet neb



95% CI = 0.25 hours to 0.77 hours

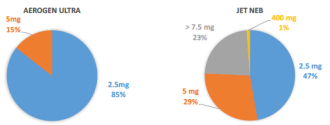
Mann-Whitney test and CI: Significance at p=0.0001

Admission Rates by Age with 95% Confidence Intervals



Albuterol Dosage

Albuterol dosage significantly lower with Aerogen Ultra p<0.001



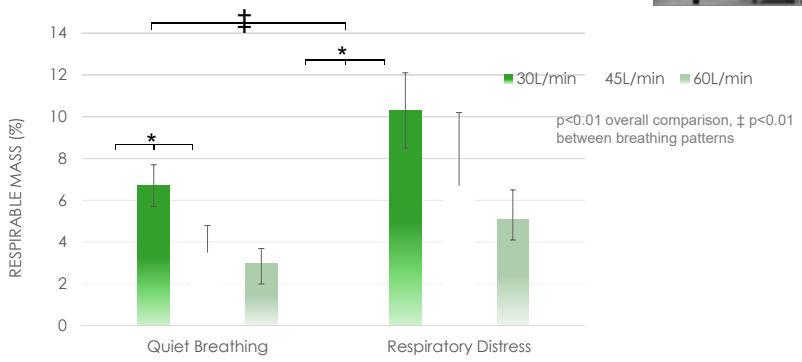
Albuterol concentration	Aerogen Ultra Albuterol Dosage	
	N	%
2.5 mg	548	85
5 mg	93	15
≥ 7.5 mg	0	0
400 mg	0	0

Albuterol concentration	Jet neb Albuterol Dosage	
	N	%
2.5 mg	416	47
5 mg	250	29
≥ 7.5 mg	203	23
400 mg	10	1

Dunne AARC 2016

Adult HFNC (In Vitro)

- In this bench model, aerosol delivery increased with respiratory distress compared to quiet breathing



- VM deposited significantly more drug in the lungs at the lower flow rate of 30 l/min than 45 l/min and 60 l/min.
- Adult model of respiratory distress (insp flow 55 L/min) compared to quiet breathing (15 l/min)
- VM demonstrated more aerosol particles with diameters of 0.4–4.4 µm, no added gas flow and a shorter nebulization duration compare to JN

17. Réminiac *et al. J Aerosol Med Pulm Drug Deliv*

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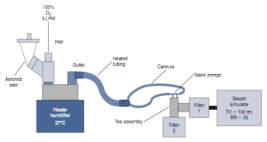
Resting Respiratory Pattern



	Inhaled Mass (n=5)	% Inhaled Dose (n=5)	Inhaled Mass (n=5)	% Inhaled Dose (n=5)	Inhaled Mass (n=5)	% Inhaled Dose (n=5)	P value
Gas/ Flow	10 L/min	10 L/min	30 L/min	30 L/min	50 L/min	50 L/min	
Oxygen 100%	.652±.16	13.2±3.6	1.644±.24	32.8±5.0	1.263±.08	25.4± 1.8	<.01*
Heliox (80/20)	.873±.15	17.4±3.1	1.757±.24	35.2± 4.7	1.501±.20	29.8±4.1	<.01*

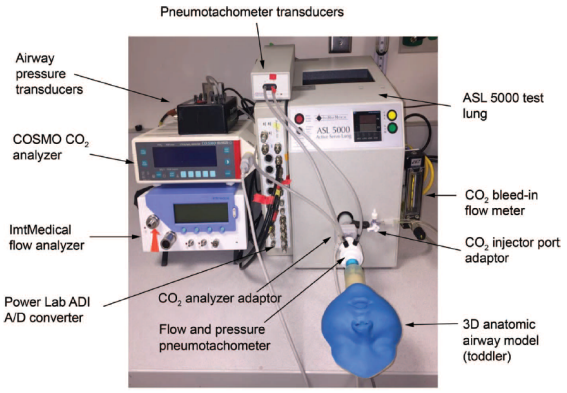
Distressed Respiratory Pattern

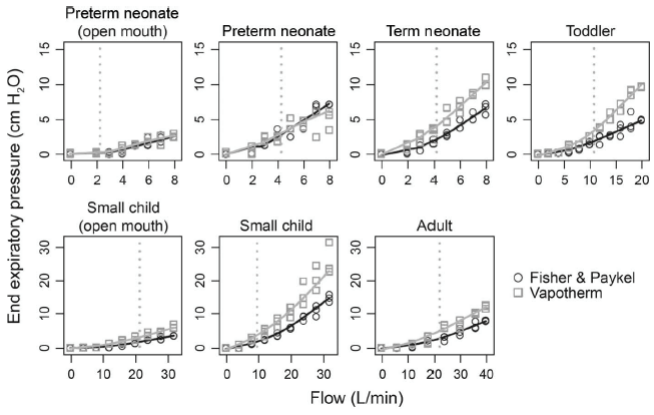
	Inhaled Mass (mg) (n=3)	% Inhaled Dose (n=3)	Inhaled Mass (mg) (n=3)	% Inhaled Dose (n=3)	Inhaled Mass (mg) (n=3)	% Inhaled Dose (n=3)	P value
Gas/ Flow	10 L/min	10 L/min	30 L/min	30 L/min	50 L/min	50 L/min	
Oxygen 100%	.667±.032	26.7±1.29	.289±.029	11.6±1.17	.088±.004	3.5±0.17	<.01*
Heliox (80/20)	.684±.059	27.4±2.37	.356±.022	14.2±0.89	.147±.43	5.88±1.73	<.01*

Dailey, Fink 2017

Effect of High-Flow Nasal Cannula on Expiratory Pressure and Ventilation in Infant, Pediatric, and Adult Models

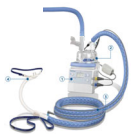
Katie R Nielsen MD MPH, Laura E Ellington MD, Alan J Gray, Larissa I Stanberry PhD, Lincoln S Smith MD, and Robert M DiBlasi RRT-NPS FAARC





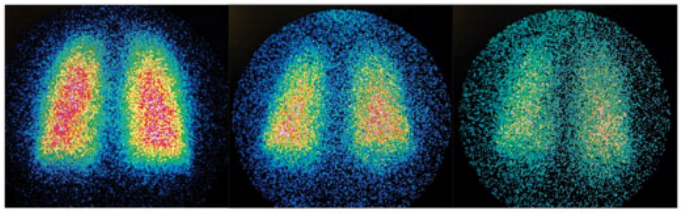
Nielson, DiBlasi
Resp Care 2017

HFNC Adult Imaging



23 healthy adults received aerosol therapy with vibrating mesh (VM) during HFNC (normal tidal breathing)

	10L/min	30L/min	50L/min
Heated	11.8 ± 4.9	3.76 ± 1.36*	2.23 ± 0.81*



*p<0.05 compared to 10L/min o
Alcoforado *et al. ISAM poster presentation* 2016

- Inverse relationship of lung deposition to flow rates

Alcoforado et al. ATS 2016

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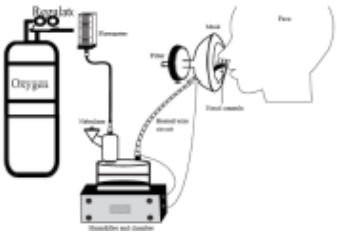
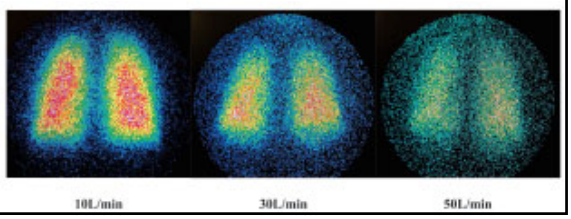
HFNC at 10, 30 and 50 L/min



	10L/min (n=08)	30L/min (n=07)	50L/min (n=08)	p-value
Lung (%)	11.81±4.90	3.76±1.36*	2.23±0.81**	0.000#
Upper airway(%)	36.46±10.49	42.46±14.43	46.72±8.58	0.213
Stomach(%)	0.25±0.10	0.69±0.75	0.23±0.32	0.118
Nebuliser(%)	10.29± 5.75	6.89± 4.37	7.63±5.63	0.437
Nasal Cannula(%)	6.51±2.46	9.76±2.47***	13.37±3.07**	0.000
Tubing(%)	16.93±4.78	19.08±8.98	16.92 ± 5.64	0.749
Chamber(%)	9.25 ± 4.33	13.08 ± 8.28	7.96 ± 1.74	0.277#
Filter (%)	8.69 ±3.09	4.23 ± 2.41*	4.90 ± 2.77**	0.011



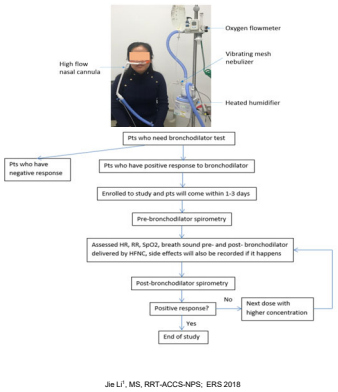
10L/min 30L/min 50L/min

Alcoforado 2016

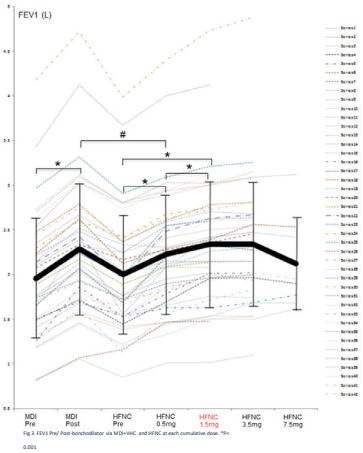
Clinical Study of Dose for Bronchodilator with HFNC

Purpose

To determine whether a cumulative bronchodilator dose during HFNC achieve similar spirometry response as pre and post bronchodilator test in PFT Lab.

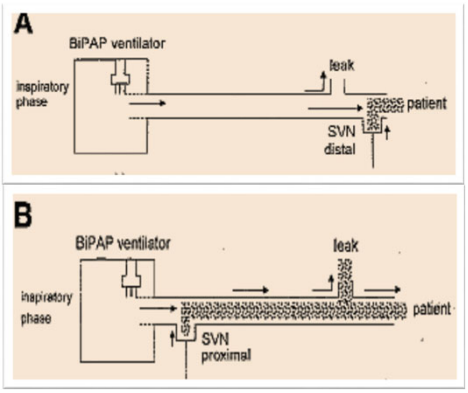


Jie Li[1], MS, RRT-ACCS-NPS; ERS 2018



- The Aerosolized bronchodilator via HFNC at 50 L/min produced a similar response as 4 Puffs MDI+VHC in these stable mild to moderate COPD ad asthma patients
- Despite reported low inhaled aerosol pulmonary efficiency with HFNC at 50 L/min, the standard label dosage of albuterol (2.5mg, US) would be sufficient starting dose while delivering albuterol via HFNC in this population

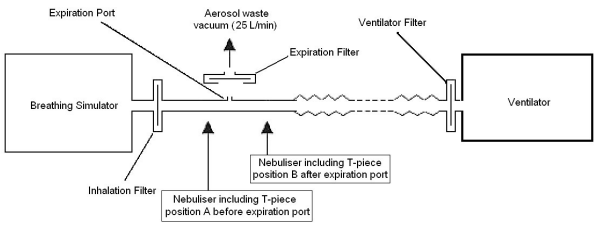
Aerosol Delivery Non Invasive Ventilation – Place neb between leak and patient



- Drug delivery influenced by:
  - Nebulizer position
  - Breathing frequency
  - IPAP/EPAP settings

Chatmongkolchart S et al *Crit Care Med* 2002;30:2515-2519.

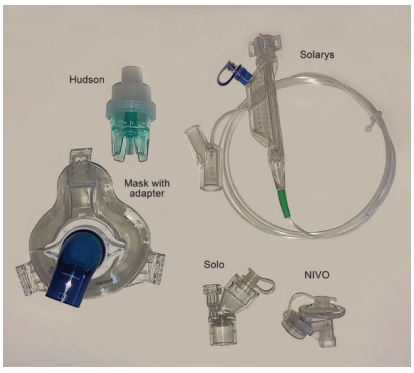
Position Neb Between Leak and Mask for best delivery



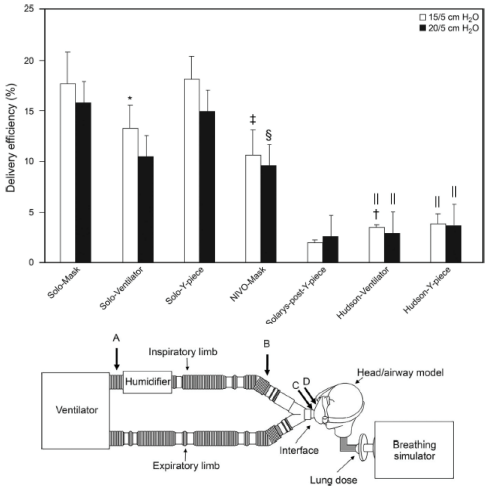
Nebulizer	Position closer to filter (A)		Position farther from filter (B)	
	Inhalation Filter (µg)	Nebulizer (µg)	Inhalation Filter (µg)	Nebulizer (µg)
Aeroneb	2573 ± 151	891 ±163	936 ± 273	1001 ± 263
Sidestream	1207 ± 161	2261 ± 795	341 ± 70	2420 ± 154

Abdelrahim ME et al *J Pharmac Pharmacol* 2010; 62;966-72.

Pediatric Non Invasive Vent with 2 Limb Circuit



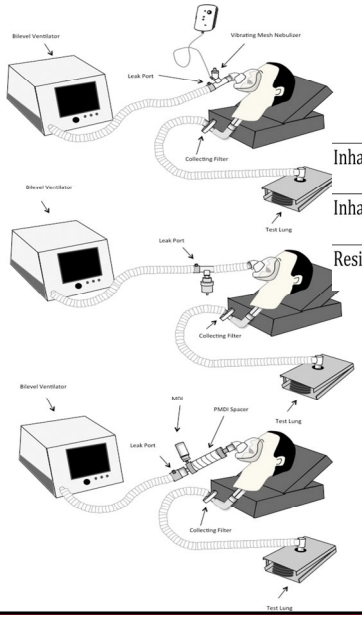
Velasco, Berlinski Resp Care 2017



EFFICIENCY OF AEROSOL DEVICES DURING NONINVASIVE POSITIVE PRESSURE VENTILATION IN A SIMULATED ADULT LUNG MODEL

Maher M. AlQuaimi BsRc RRT, James Fink PhD, RRT, FAARC, FCCP, Robert Harwood,MSA,RRT,Meryl M Sheard MSc RPFT, Arzu Ari, PhD, RRT, PT, CPFT,FAARC
Georgia State University, Atlanta, GA

Experimental setup used with VMN, JN, and pMDI

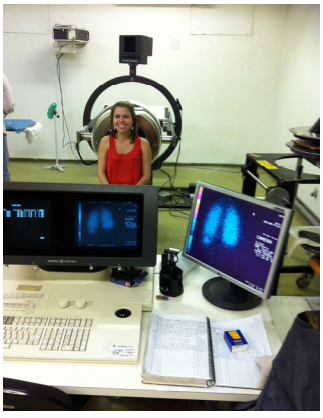


	JN	VMN	pMDI-N	pMDI-R
Inhaled Mass (mg)	0.33 ± 0.02	0.72 ± 0.05	0.10 ± 0.01	0.09 ± 0.01
Inhaled Mass Percent (%)	13.12 ± 0.72	28.83 ± 1.93	23.53 ± 2.03	21.38 ± 0.32
Residual volume (ml)	1.65 ± 0.14	0.10 ± 0.07		

Vibrating Mesh (VMN) > 2 fold more than Jet

VMN and pMDI similar dose efficiency

Lung Dose JN vs Mesh



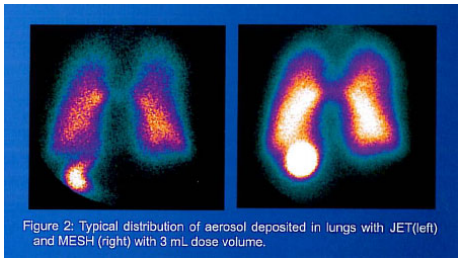


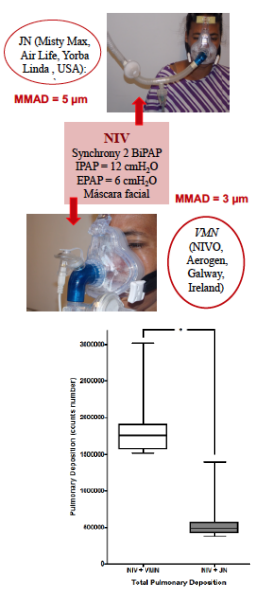
Figure 2: Typical distribution of aerosol deposited in lungs with JET(left) and MESH (right) with 3 mL dose volume.

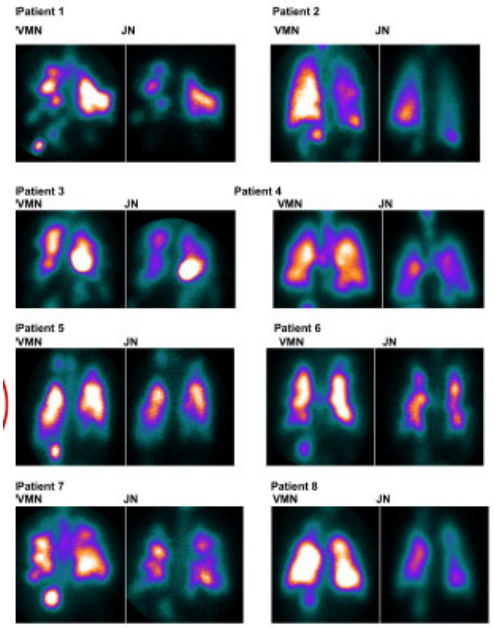
Lung deposition (corrected for absorption) with the Mesh was > 3 fold greater than JN, independent of dose volume used with the MESH.

Neb/Dose	JET NEB 3 mL	MESH 3 mL
Total Lungs	1.97 ± 0.8%	8.26 ± 1.1 %*
Inhaled Dose	7.31 ± 4.3%	27.3 ± 10.1 %*

*p<0.0001 (MESH 3 mL vs JN 3 mL) and
**p<0.007 (MESH 1 mL vs JN 3 mL).

NIV – VMN vs JN – COPD Patients

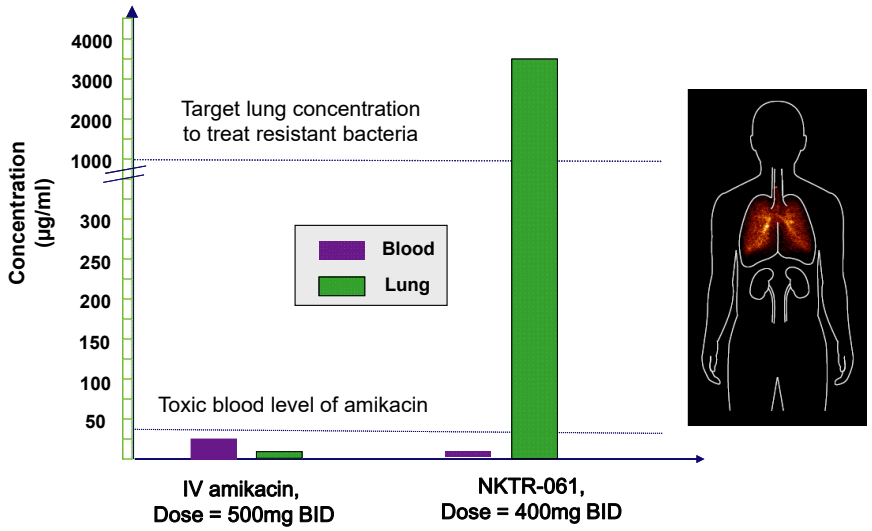




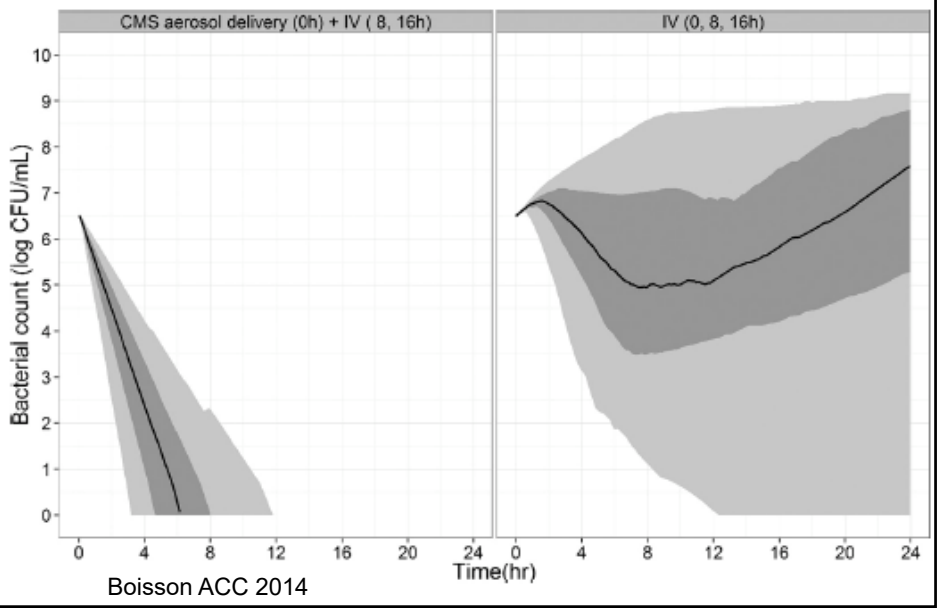
Galindo-Filho In press

Pulmonary Drug Delivery System – Amikacin Inhale®

Delivery of inhaled amikacin during mechanical ventilation targets the lung without systemic toxicity



Colistin by Aerosol + IV vs IV Alone



Boisson ACC 2014

Conclusion

- Many inhaled drugs were approved based on studies in spontaneous breathing subjects with lung doses of 10 – 20%.
- Lung dose with standard JN can deliver as little as 3% of dose to the lung.
- Many of the devices used in Neonates, infants, children and adults can achieve >10% lung dose with conventional ventilation, NIV and HFNC.
- Choice of aerosol generator and placement makes a difference in drug delivery to the lung
- Selection of Drug Dose for Specific Device can Achieve Effective Lung Doses

JFINK@aerogenpharma.com

LARGE GROUP: VENTILATOR MANAGEMENT 2
Case Examples in ARDS and Respiratory Failure

Friday, January 18, 2019 – 3:45 p.m. – 4:30 p.m.

Lance Pangilinan, RRT
UC San Francisco
Adult Critical Care Respiratory Therapist

Lance Pangilinan, RRT, is an Adult Critical Care Respiratory Therapist for the University of California San Francisco, Department of Anesthesia at Zuckerberg San Francisco General Hospital and Trauma Center (ZSFG). There, he currently serves as a bedside therapist and educator. Lance is a lecturer for the Critical Care Residency Program at ZSFG on the topics of Mechanical Ventilation Mechanics and ARDS management. He is a published researcher and has spoken nationally at a number of respiratory and critical care conferences on the subjects of strategic ventilation practices and the use of non-invasive end-tidal monitoring.

Justin Phillips, RRT
UC San Francisco
Adult Critical Care Respiratory Therapist

Justin Phillip, RRT, is an Adult Critical Care Respiratory Therapist for the University of California San Francisco, Department of Anesthesia at Zuckerberg San Francisco General Hospital and Trauma Center (ZSFG). There, he currently serves as a bedside therapist and educator. Justin is a lecturer for the Critical Care Residency Program at ZSFG on the topics of Mechanical Ventilation Mechanics and ARDS management. Additionally, he is Adjunct Faculty for the Respiratory Care Program at Ohlone College for Health Sciences and Technology. Justin is a published researcher and has spoken nationally at a number of respiratory and critical care conferences on the subjects of strategic ventilation practices and the use of non-invasive end-tidal monitoring.

Gregory Burns, RRT
UC San Francisco
Respiratory Care Practitioner

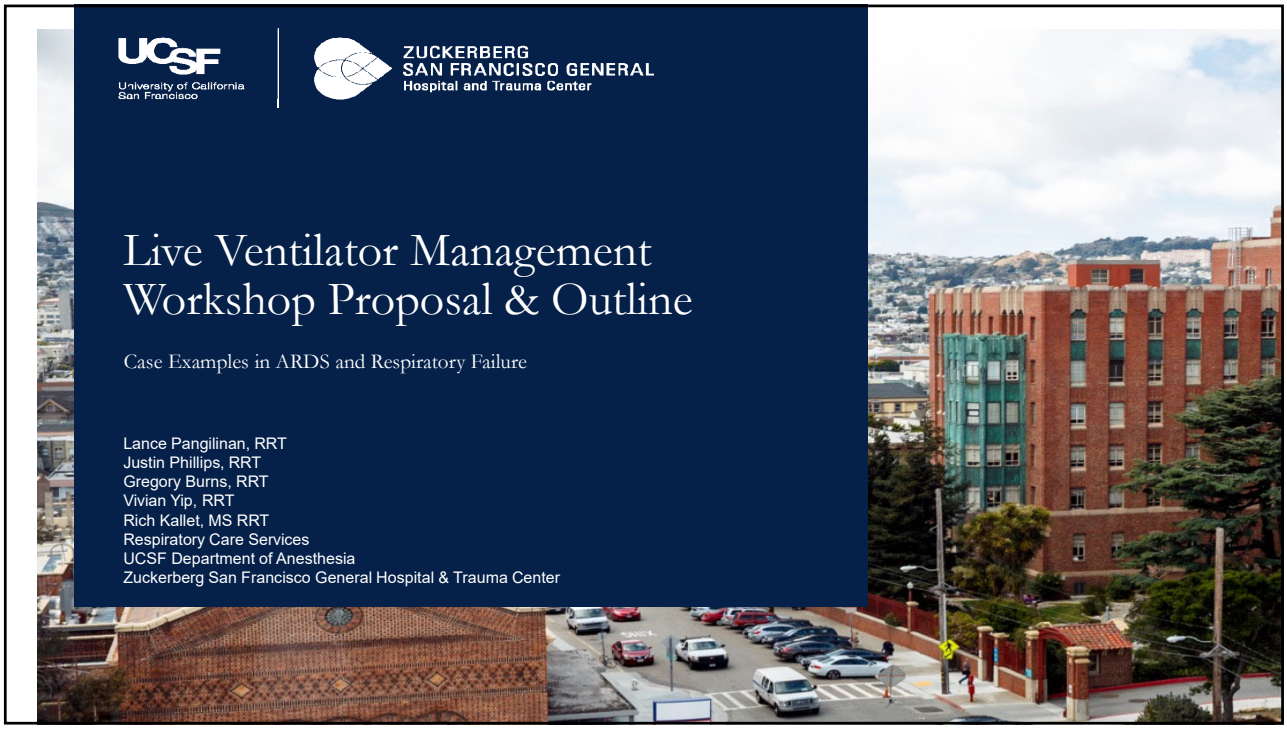
Gregory Burns, RRT, is a Respiratory Care Practitioner for the University of California San Francisco, Department of Anesthesia at Zuckerberg San Francisco General Hospital and Trauma Center (ZSFG). There, he currently serves as interim Equipment Manager. Gregory's research interests include the effect of inhaled vasodilators on patients with the Acute Respiratory Distress Syndrome.

Vivian Yip, BS, RRTACCS
UC San Francisco
Adult and Neonatal Critical Care
Respiratory Therapist

Vivian Yip, BS, RRT-ACCS, is a Adult and Neonatal Critical Care Respiratory Therapist for the University of California San Francisco, Department of Anesthesia at Zuckerberg San Francisco General Hospital and Trauma Center (ZSFG). There, she currently serves as a bedside therapist and educator. Vivian is a lecturer for the Critical Care Residency Program at ZSFG on the topics of Mechanical Ventilation Mechanics and ARDS management. Vivian is a published researcher and has spoken at a number of respiratory and critical care conferences on the subjects of spontaneous breathing trials and the impact of THAM in patients with severe acidosis in ARDS.

Rich Kallet, MS, RRT
UC San Francisco
Respiratory Therapist

Rich Kallet, MS, RRT received his baccalaureate degree in respiratory therapy from SUNY Upstate Medical University in Syracuse NY and his masters of sciences degree in health sciences from San Francisco State University. He spent the majority of his 42 year career working for the University of California, San Francisco Department of Anesthesia at San Francisco General Hospital and the UCSF Cardiovascular Research Institute. He was a research coordinator for NIH ARDS Network from 1996-2011 and has worked as a project manager and director of clinical research for the CVRI, the San Francisco Injury Center and both the Critical Care Management Group and the Respiratory Care Services at SFGH. He retired in 2018 and currently is section editor for the Respiratory Care Journal.



Overview

- Forty-five (45) minute interactive panel discussion and case review on Acute Respiratory Distress Syndrome (ARDS), integrating recreated live simulated clinical scenarios via a high-fidelity lung model to a live audience

Overview

- Introduction to Acute Respiratory Distress Syndrome (ARDS) & ventilator graphics
- Clinical application and interpretation of driving pressure (ΔP)
- Stress index and lung mechanics during mechanical ventilation
- Prone positioning and mechanics in relation to clinical outcomes

Introduction to Acute Respiratory Distress Syndrome (ARDS) & Ventilator Graphics

Zuckerberg San Francisco General
UCSF

Introduction to ARDS & Ventilator Graphics

- What we currently know
- Current state of management
- 2017 ATS Clinical Practice Guidelines & Recommendations for ARDS management

Case: Background

- 34 y/o male with a PMH of pancreatitis (Dx 4 months prior) presented to our Emergency Department hypertensive, tachycardic, and febrile. He complained of radiating epigastric pain to his back. Upon physical assessment, he was nauseous, had a distended abdomen, and subsequently vomited. He was initially admitted to our medical ICU for medical management of acute alcoholic pancreatitis.

Case: Background

- Transferred to surgical service due to development of acute abdominal compartment syndrome and sepsis.
- Developed acute respiratory failure during initial fluid resuscitation. Intubated for Type I & II respiratory failure. As his hospitalization progressed, he further developed ARDS and multi-organ system failure.
- ECMO referral service declined intervention due to lack of supporting clinical outcome evidence in acute pancreatitis (2014).

Summary of Hospital Course

- 66 days of MV
- 48 days of prone positioning
- 53 days to spontaneous breathing
- 12 days of spontaneous breathing pre extubation GB1

Slide 8

GB1 Can you please verify that this is true?
Gregory Burns, 12/1/2018

Key case points

- Utilizing and applying the concept of driving pressure in lung mechanics when tailoring mechanical ventilation in ARDS
- Clinical relevance in stress index when assessing lung mechanics in ARDS
- Use of prone positioning and assessment of efficacy

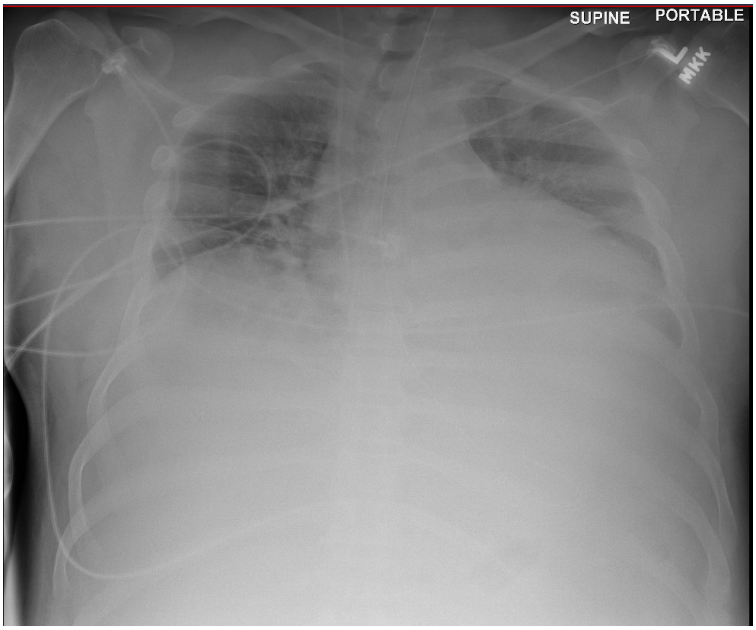
GB3

DAY 1

- Admitted to ICU on 3L NC.
- Intubated 2/2 altered mental status
- Vent settings
  - VC: VT = 510mL(8mL/kg), RR = 18, PEEP = 10cmH20, I-Time = 0.85(I:E = 1:4.0), Fi02 = 1.0
- Initial Vent Measures:
  - PIP = 41cmH20
  - Pplat = 30cmH20
  - MAP = 17cmH20
  - MV = 9.1L/min
  - Cstat = 26
  - PetCO2 = 46
  - Driving Pressure = 20cmh20
- ABG results: 7.25/50/86/21.9/-5.3
- ARDSnet started for LPV
  - Berlin Score = 86 (Severe)
  - Vent Settings: VC: VT = 390mL(6mL/kg), RR = 24, PEEP = 10cmH20, I-Time = 0.85, Fi02 = 1.0

Slide 10

GB3 This is my recommendation for how to configure this slide by reducing the total amount of words
Gregory Burns, 12/1/2018



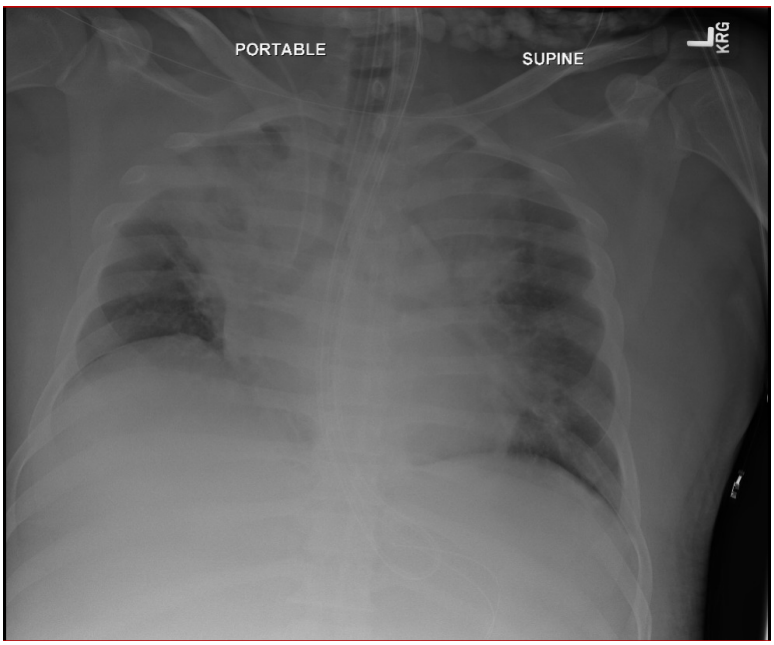
Day 1 Continued

- Initial 24 hours
  - Unstable PaO2/FiO2 (46-80)
    - C_{RS} related to severe ARDS
    - Severe asynchrony
    - increasing abdominal pressures 2/2 compartment syndrome
- Tx's considered
  - NMBA
  - Adaptive pressure control
  - PEEP- 16 -24cmh20 in efforts to improve C_{RS} and P/F ratio while combatting hypotension
  - RM- ↔ PaO2/FiO2 and aborted 2/2 hypotension
  - PGI2- ↔ PaO2/FiO2
- Eventual OR- abdominal decompression ↓ 2 L of fluid which initially showed some improvement in C_{RS}, but C_{RS} worsened shortly after once again

GB4

Prone Positioning

- PRONE positioning day 1- x9h
  - ABG Pre Prone: 7.31/54/66//27.2/+0.9 (P/F ratio: 66)
    - Vent Settings: PRVC: VT = 390(6mL/kg), RR = 26. PEEP = 18cmh20, I-Time = 0.80(I:E = 1:1.8), Fi02 = 1.0
  - ABG Post prone x 9 hours (supine): 7.36/52/182/29.4/+4.0 (P/F ratio: 182)
    - Vent Settings: PRVC: VT = 320(5mL/kg), RR = 34. PEEP = 20cmh20, I-Time = 0.70(I:E = 1:1.5), Fi02 = 1.0



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UCSF

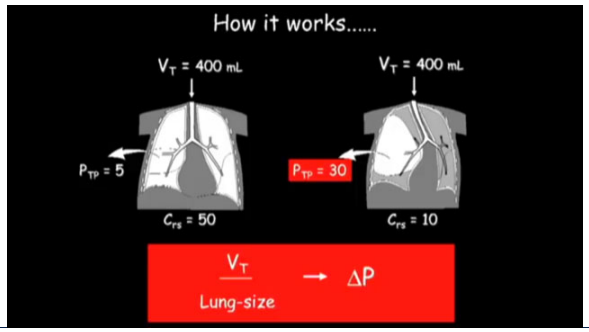
Slide 13

GB4 We should have a prone ABG here \
Gregory Burns, 12/1/2018

Clinical Application & Interpretation of Driving Pressure (ΔP)

Clinical Application & Interpretation of ΔP

- Overview
  - What is it?
    - It is the ratio between VT and the static compliance of the respiratory system resembling the lung and chest wall elastance and has a direct relationship with Transpulmonary Pressure (P_{TP})
    - In short, the corrected VT for the patient's Static Compliance



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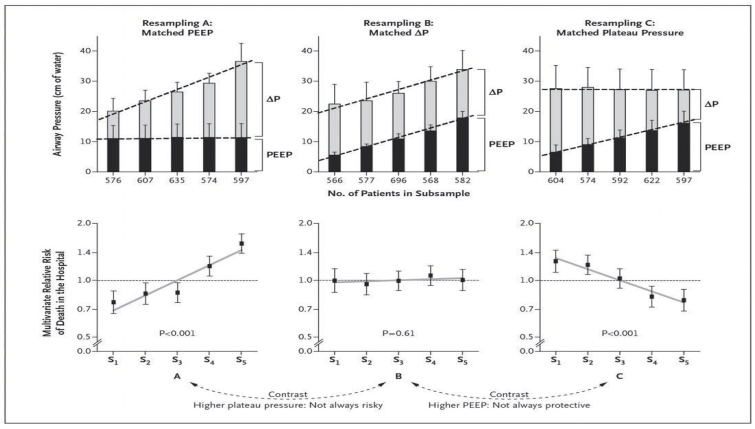
N = 3,500

The NEW ENGLAND JOURNAL of MEDICINE

Driving Pressure and Survival in the Acute Respiratory Distress Syndrome

Amato et al

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



Briefly go over w/ audience the Amato study and how mortality reduced by 22%

UCSF

How do we calculate driving pressure?

$$C_{RS} = \frac{V_T}{P_{PLT} - PEEP}$$

C_{RS} Equation

$$\Delta P = \frac{VT}{C_{RS}}$$

Driving Pressure Equation

$$\Delta P = \frac{V_T}{C_{RS}} \quad \frac{V_T}{P_{PLT} - PEEP}$$

$$\Delta P = \frac{V_T}{\frac{V_T}{P_{PLT} - PEEP}}$$

$$\Delta P = \frac{V_T}{V_T} \cdot (P_{PLT} - PEEP)$$

$$\Delta P = P_{PLT} - PEEP$$

UCSF

How do we manage the Ventilator w/ DP?

Talk to audience about strategies
- VT adjustments (LPV remains the current therapy)
- Do we still worry about Pplats? (Yes!)

Look at scenarios using ASL 5000/ Ventilator

Stress index and lung mechanics during mechanical ventilation

Stress index and lung mechanics during mechanical ventilation

- Overview
  - ➢ What is it?
- We use Stress Index:
  - To help us prevent Ventilator Induced lung Injury by gauging tidal recruitment vs. hyperinflation by evaluating the Paw-Time curve graphics
- Stress Index Equation was created using the Levenberg- Marquardt algorithm which is preprogramed in a computer software: Paw = a (T0 – T1) +b
  - T0 – T1 = The time from beginning to end of the curve shape.
  - Quick way to gauge is to just look at the shape of the Paw-time curve

Airway pressure-time curve profile (stress index) detects tidal recruitment/hyperinflation in experimental acute lung injury

Salvatore Grasso, MD; Pierpaolo Terragni, MD; Luciana Mascia, MD, PhD; Vito Fanelli, MD; Michel Quintel, MD; Peter Herrmann, PhD; Goran Hedenstierna, MD; Arthur S. Slutsky, MD; V. Marco Ranieri, MD

Objective: **To evaluate whether the shape of the airway pressure-time (Paw-t) curve during constant flow inflation corresponds to radiologic evidence of tidal recruitment or tidal hyperinflation in an experimental model of acute lung injury.**

Design: **Prospective randomized laboratory animal investigation.**

Setting: **Department of Clinical Physiology, University of Uppsala, Sweden.**

Subjects: **Anesthetized, paralyzed, and mechanically ventilated pigs.**

Interventions: **Acute lung injury was induced by lung lavage. end-expiratory pressure and V_T were both increased to obtain $1.3 > b > 1.1$ and $1.5 > b > 1.3$. Experimental conditions sequence was random.**

Measurements and Main Results: **Pulmonary computed tomography was obtained during end-expiratory and end-inspiratory occlusions. Tidal recruitment was quantified as nonaerated (between −100 and +100 Hounsfield units) lung area at end-expiration minus end-inspiration. Tidal hyperinflation was quantified as hyperinflated (between −900 and −1000 Hounsfield units) lung area at end-inspiration minus end-expiration. Computed tomography images showed that tidal recruitment and tidal hy-**

Report to audience some evidence behind SI briefly

Ferrando *et al. Critical Care* (2015) 19:9
DOI 10.1186/s13054-014-0726-3

CRITICAL CARE

RESEARCH Open Access

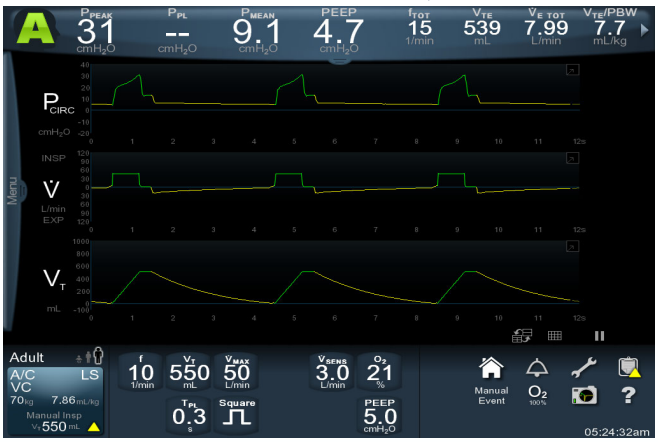
Adjusting tidal volume to stress index in an open lung condition optimizes ventilation and prevents overdistension in an experimental model of lung injury and reduced chest wall compliance

Carlos Ferrando[1*], Fernando Suárez-Sipmann[2,3], Andrea Gutierrez[1], Gerardo Tusman[4], Jose Carbonell[1], Marisa García[1], Laura Piqueras[5], Desamparados Compañ[6], Susanie Flores[7], Marina Soro[1], Alicia Llombart[8] and Francisco Javier Belda[1]

Do we need particular settings to assess SI?

Show audience scalars on Vent

- Ventilator criteria to assess SI:
  - Look at Pressure-Time curve
  - Volume –cycled mode of ventilation
  - Constant flow pattern



What is normal vs. abnormal?

Using the ASL 5000, will go over stress indexes and give an example on corrective measures (Ex: adjusting VT)

- **Optimal Stress Index range: 0.9 – 1.1**
- **Stress index neutral value is set at 1 which appears linear(straight) on the Paw-Time curve**
  - **SI < 1 = Indicates that compliance is increasing w/ time which is indicative of tidal recruitment**
    - **Paw-Time curve appears convex**
  - **SI > 1 = Indicates that compliance is progressively decreasing w/ time which is indicative of over distension**
    - **Paw-Time curve appears concave**

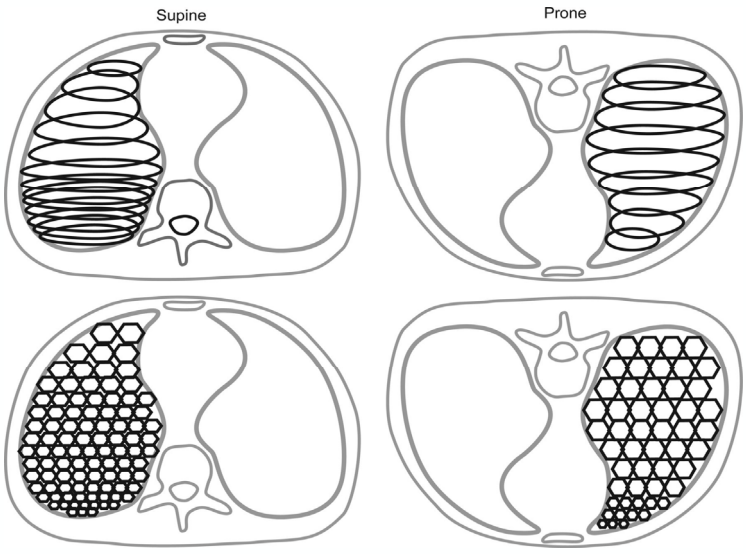
Prone Positioning

Prone Positioning

- PROSEVA Study 2013
  - Multicenter, prospective, randomized, controlled trial
  - Inclusion criteria
    - P/F ratio < 150 mmHg
    - FiO_2 ≥ 0.60
    - PEEP ≥ 5 cmH20
  - Mean duration of prone: 17±3 hours
  - 28 day mortality (p<0.001)
    - Prone: 16.0%
    - Supine: 32.8%
  - 90 day mortality (p<0.001)
    - Prone: 23.6%
    - Supine: 41.0%

Prone Positioning- Continued

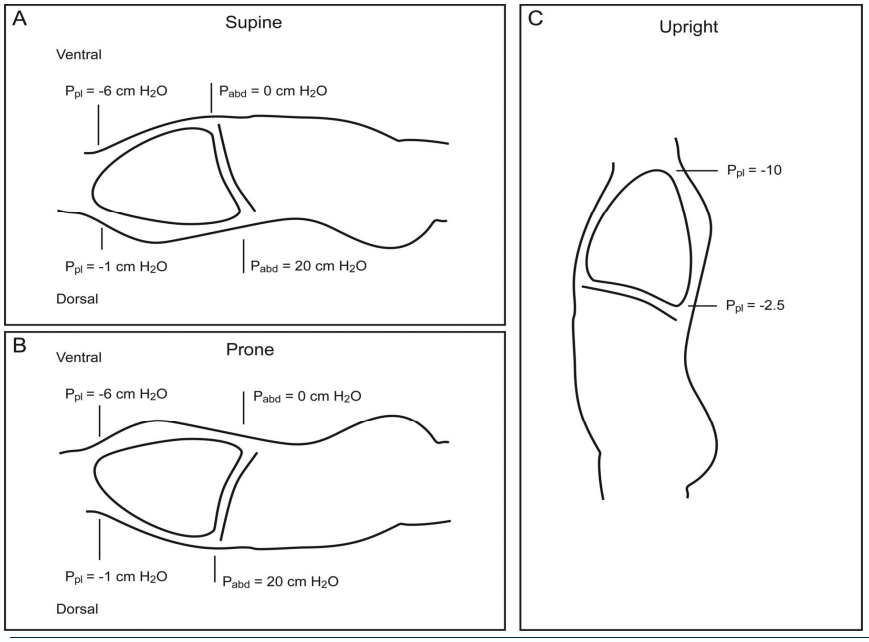
- Reduces shunt and increases FRC
  - Prone positioning, as compared with supine positioning, markedly reduces the overinflated lung areas while promoting alveolar recruitment.
  - May help prevent ventilator-induced lung injury by homogenizing the distribution of stress and strain within the lungs.
  - Transpulmonary pressure along the ventral-to-dorsal axis is more homogeneously distributed in the prone position than in the supine position



- Schematic representation of strain-stress distribution and its impact on alveolar size distribution between the supine and prone position. The Slinky effect of a triangular-shaped spring suspended from its apex (supine position) causes higher strain and larger variation in the distribution of alveolar sizes due to the effects of gravity and a steeper stress production during mechanical inspiration in the upper lung regions.
- In contrast, suspending the spring by its base across a wider surface area (prone position) produces a more even strain and more homogeneous distribution of alveolar size that lessens inhomogeneity in stress development throughout the lungs during mechanical inspiration.

Prone Positioning on Chest Mechanics

- Both pleural pressure (P_{PL}) and intra-abdominal pressure (IAP) change with body position which influences the shape and position of the diaphragm.
- In supine position, the hydrostatic pressures in the abdominal compartment exceed those in the chest cavity by a factor of 5.
- Disparities in hydrostatic pressures between these compartments are magnified further with hypervolemia resulting in abdominal distension.
- The highest IAP is measured in the dorsal regions and is transmitted to the pleural space, thus acting to compress the dorsocaudal regions of the lung.



Schematic representation of vertical pleural pressure (Ppl) distribution from the apex to the bases in the upright position and their respective diminishment in the recumbent supine and prone position.

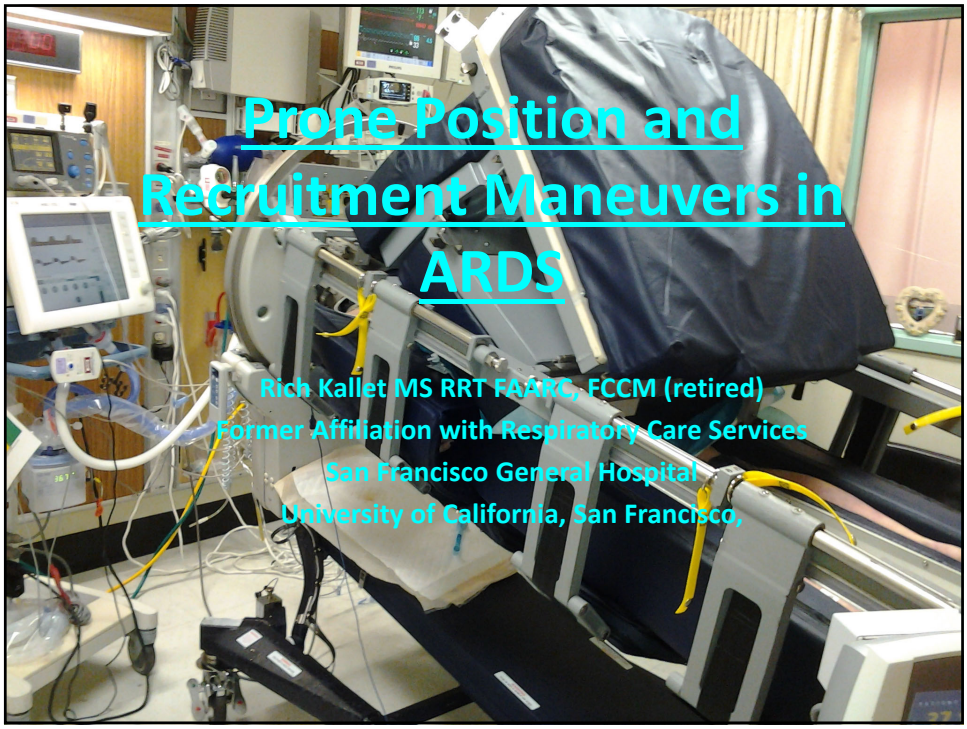

UCSF
Presentation Title

PRONE POSITIONING, RECRUITMENT MANEUVERS

Rich Kallet, MS, RRT
UC San Francisco
Respiratory Therapist

Friday, January 18, 2019 –4:30 p.m. – 5:15 p.m.

Rich Kallet, MS, RRT received his baccalaureate degree in respiratory therapy from SUNY Upstate Medical University in Syracuse NY and his masters of sciences degree in health sciences from San Francisco State University. He spent the majority of his 42 year career working for the University of California, San Francisco Department of Anesthesia at San Francisco General Hospital and the UCSF Cardiovascular Research Institute. He was a research coordinator for NIH ARDS Network from 1996-2011 and has worked as a project manager and director of clinical research for the CVRI, the San Francisco Injury Center and both the Critical Care Management Group and the Respiratory Care Services at SFGH. He retired in 2018 and currently is section editor for the Respiratory Care Journal.



Prone Position and Recruitment Maneuvers in ARDS

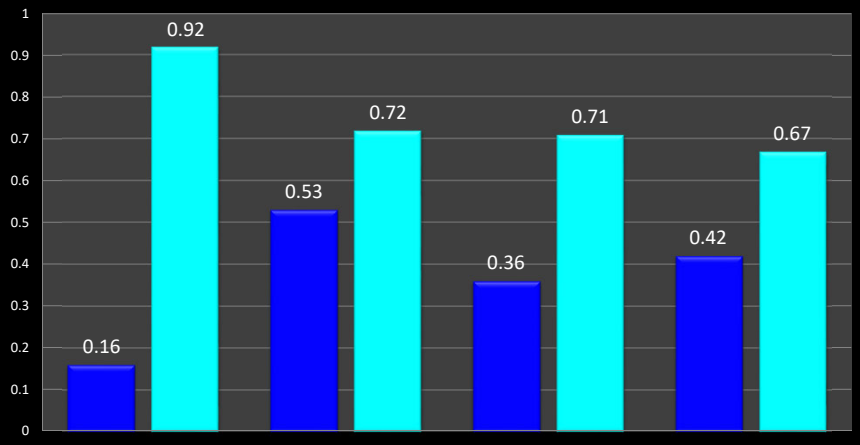
Rich Kallet MS RRT FAARC, FCCM (retired)
Former Affiliation with Respiratory Care Services
San Francisco General Hospital
University of California, San Francisco,

COI Statement

- Affiliation with the Asthma and Allergy Prevention Company McClellan Park, CA

Case Study #1

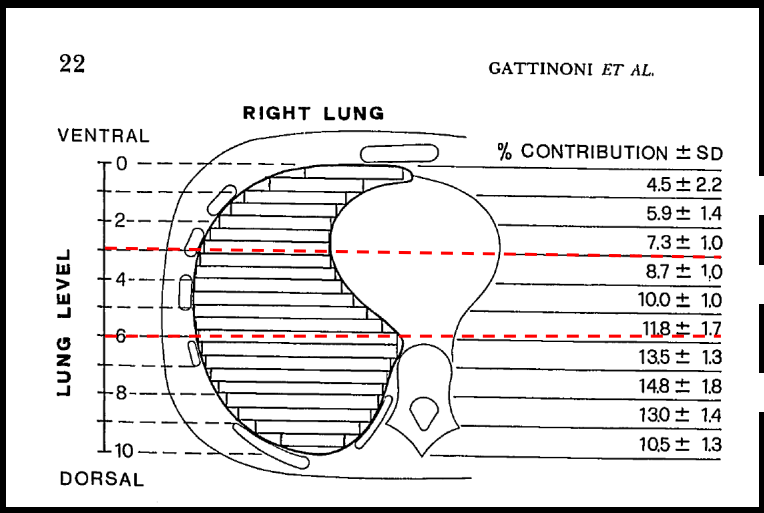
- A 39 yo F admitted to SFGH TICU s/p hanging, cardiac arrest, massive aspiration, severe hypoxemia, asynchrony and hemodynamic instability.
- Pre-prone management:
  - NMBA & Aeroprost 50 ng/kg/m
  - V_T: 530 mL (8.5); V_E:**17L/m**
  - Pplat: 31 cmH_2O; Crs: 33 mL/cmH_2O
  - PEEP: +15, F_{iO2}: 0.90 → ABG: 7.28 / **66**/ 105
  - P/F = 117 ; V_D/V_T = **0.92**, a/AP_{O2} = 0.16



		1h	2h	20h
P/F	117	351	232	**265**
FiO2	0.90	0.90	0.60	**0.50**

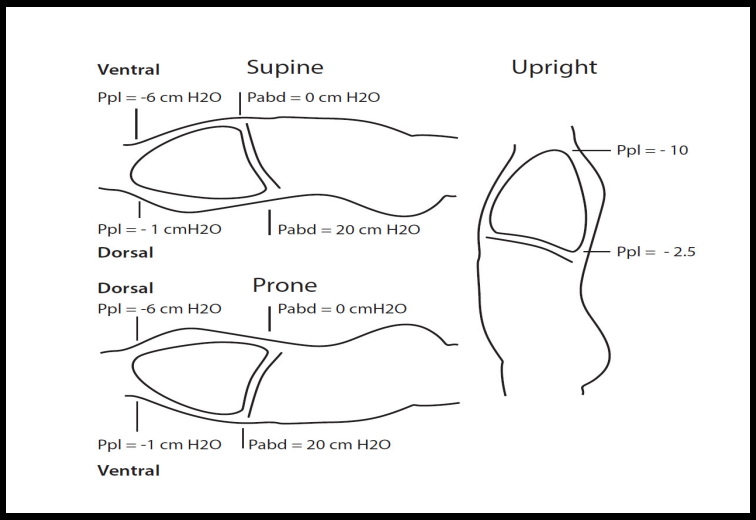
How do we explain the effects of prone positioning on gas exchange in ARDS?

Percent Contribution of Ventral-Dorsal Lung Level to Total Area of the Lung by CT Analysis

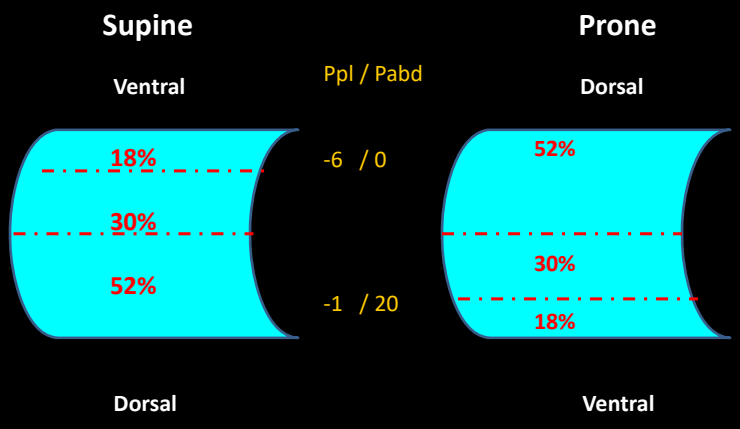


Gattinoni Anesthesiology 1991

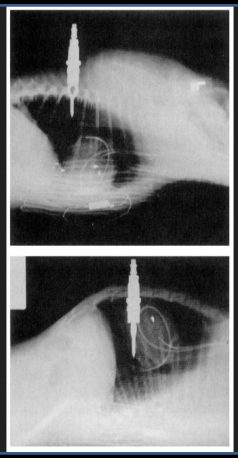
Prone Position Reverses the Pleural Pressure Gradient



Distribution of Lung Tissue Supine vs. Prone



Increased Dorsal:Caudal Ventilation with Prone Position

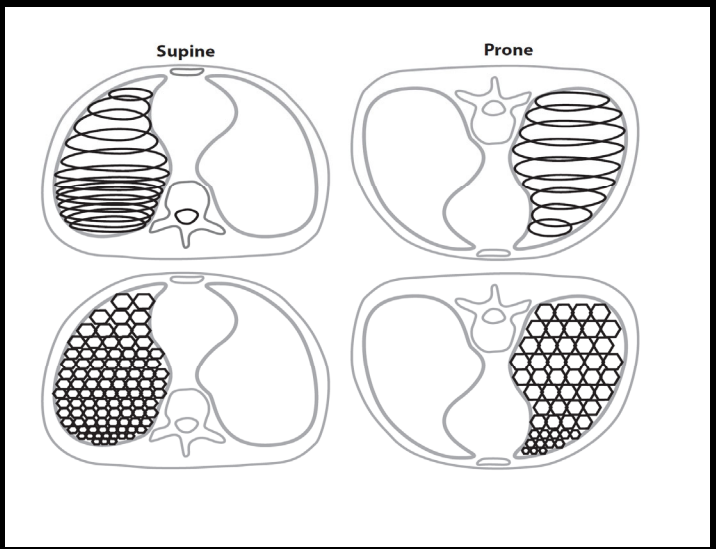


PRONE

SUPINE

Broccard et al. Crit Care Med 2000

Pulmonary Stress-Strain: Supine vs. Prone Position



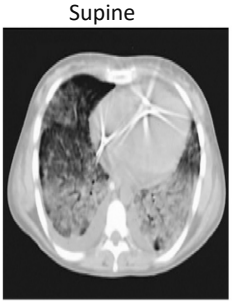
Summary: Δ In Ventilation:Perfusion Relationships Prone vs. Supine

- More even pleural pressure distribution down the lung → more even ventilation distribution
  - heart falls against the sternum & decompresses the LLL
  - More even stress distribution: larger dorsal mass of the lung suspended along larger dorsal chest wall.
  - Ventral shift of abdominal contents: ↓ resistance dorsal CW
  - Dominant dorsal lung perfusion remains intact with increased ventilation distribution when assuming the prone position
- ↑ V/Q Matching & Enhanced Recruitment

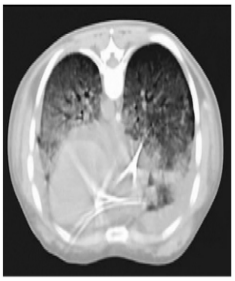
Complexity of Pulmonary Perfusion

- Whole Lung Level: Gravity: **Hydrostatic Pressures**
  - ↑lung tissue dorsal-caudal regions →↑vascularity →↑ perfusion/unit lung volume (upright position) ~30% determinant
- **Intermediate Level: Vascular tree geometry dominant**
- 23 generations **uneven branching angles/diameters that mimic airway structures (fractal geometry)**
- Heterogenous perfusion within horizontal tissue plane as well as vertical zones
- Perfusion is largely **independent of gravity** : regardless of body posture, **perfusion is always greater in dorsal lung regions** (an"anatomical flow bias favoring dorsal perfusion", ↑ local NO production in the dorsal lung)

Supine



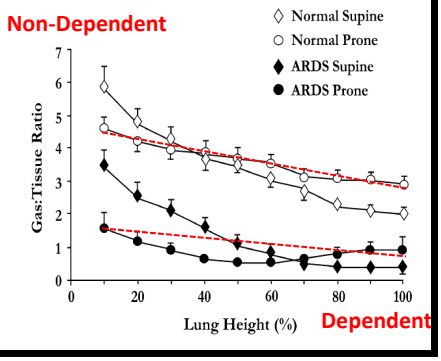
Prone:



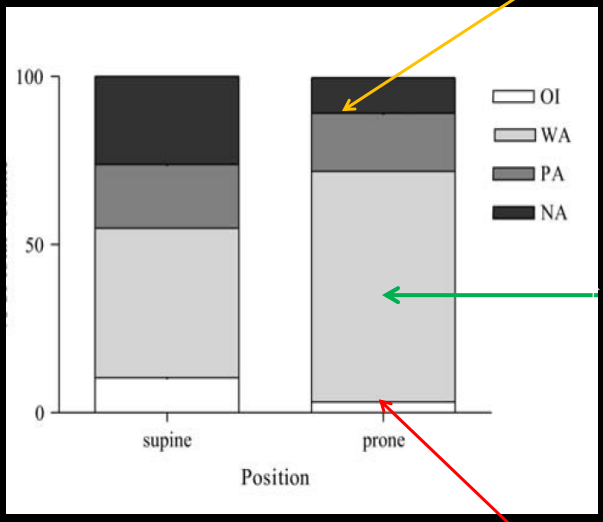
Redistribution of Compressive Forces in ARDS

"At each [CT scan] level, the amount of tissue mass in ARDS was almost **double** that in normal subjects."
"Moreover, the inflammatory cell activity appears present throughout the whole lung independent of the inflation status."

"In ARDS, where the **lung is 2-3 times heavier** than normal, in the supine position the potentially open alveoli in the dorsal dependent region collapse".
Gattinoni ,2013



Prone Positioning as LPV



↓ Nonaerated

Well Aerated

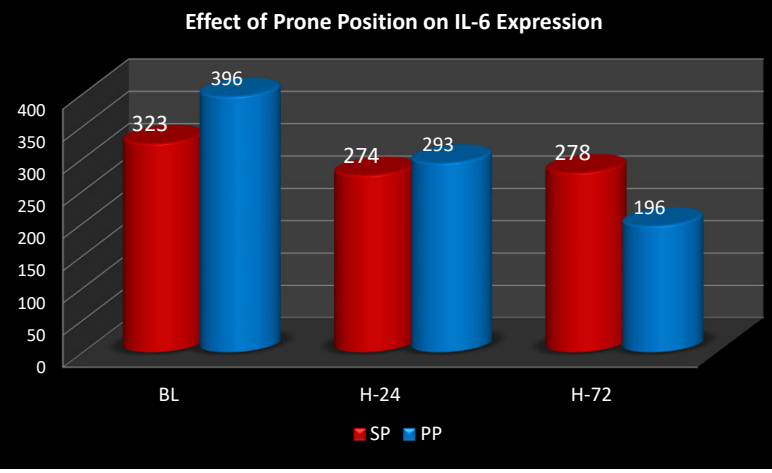
↓ Overinflation

Galiatsou 2006

Prone Positioning Greatly Reduces Pro-Inflammatory Mediator Release in ARDS

Chan (2007): RCT (N=22) ARDS-CAP, **72h PP**

Mortality on ARDS Day 14 predicted by IL-6 (378 vs. 206 pg/mL)



Impact of PP in ARDS

(33 observational studies since 1976)

- **N = 735**
- Responders: 80% [57-100%]
- + Response Early & Late; $ARDS_{pulm}$ & $ARDS_{extpulm}$
- ↑Pa_{O2}: 40 [26-52]; ↑Pa_{O2}/Fi_{O2}: 67 [8-161]
- No Δ hemodynamics most patients (2-4%)
- ↑ secretion mobilization some patients
- Mixed results: effects on Pa_{CO2}, Crs, EELV

PROSEVA Study

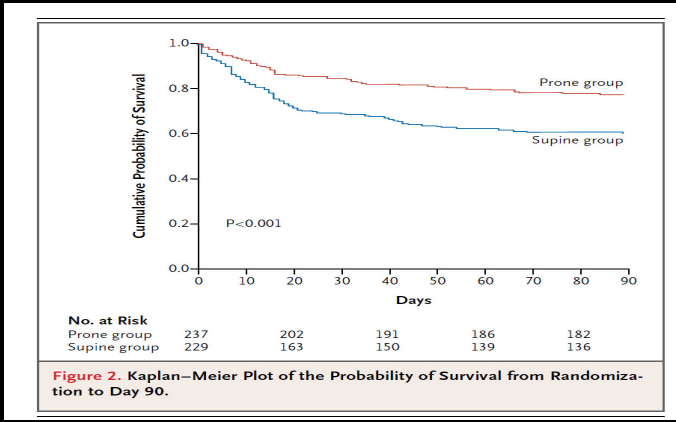


Figure 2. Kaplan–Meier Plot of the Probability of Survival from Randomization to Day 90.

Multi-center RCT N = 466: 90 Day mortality ↓ 41 to 24%
Adjusted RR for mortality 0.48 (SOFA);
↑ VFD 4 & 14 (D-28,D-90)
↑ No difference in complication rates

N Engl J Med 2013

Meta-Analyses of RCTon ↓Mortality

- **Sud (2010)** : when P/F < 100 (RR: 0.84) effect to P/F 140
- **Lee (2014):** RR: 0.77, + Effect: P/F < 150 (RR: 0.72) , PP > 10h (RR: 0.62)
- **Beiter (2014):** RR: 0.66 *only when* $V_T \leq 8$ *mL/kg* and when PP ≥ 12h/day (RR: 0.71)

  ↓Baseline VT 1mL/kg ↓ risk 16.7%

  Hu (2014): when P/F ≤ 100 (RR: 0.71); PEEP≥ 10 (RR: 0.57)

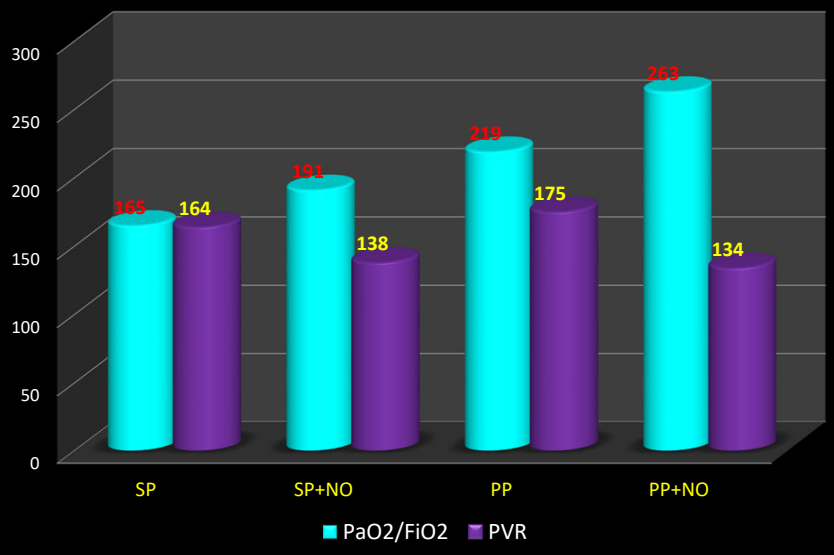
  and PP > 12h/day (RR: 0.54)

Prone Positioning Unloads the Right Ventricle & Decreases PFO-Related Shunt

- **Cor-Pulmonale: 22% of ARDS cases**
  - ARDS+Cor-Pulmonale 60% vs. 36% Mortality
  - PP in ARDS pts w/ Cor-Pulmonale
  - 33% ↓RV size/ 18h in PP; ↑CI 2.9 to 3.4
  - Associated w/ ↑oxygenation, ventilation, Crs
- **PFO: ~20% of ARDS case related to Cor-Pulmonale**
  - Case Report of severe PFO by TE-Echocardiography
  - PP immediate ↓ in bubble emboli transversing artia &
  - ↑ Pa_{O2}/Fi_{O2} 59 to 278 mmHg; ↓ Pa_{CO2} 54 to 30 mmHg

Viellard-Baron 2007 Cor Pulmonale; Legras 1999 PFO

PP Enhances Inhaled Vasodilators in ARDS

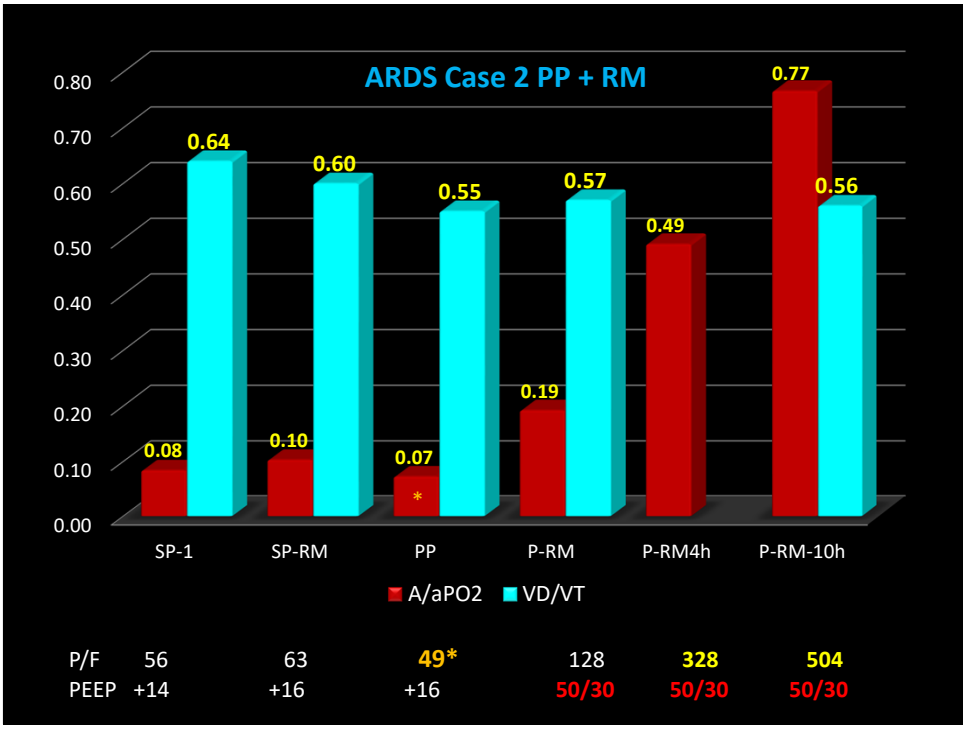


Johannigman 2001

Recruitment Maneuvers & Prone Position

Effects of adding RM to PP

- **ARDS Case 2**
- 39 yo obese male (BMI = 32) aspiration (Sp_{O2} = 60% on RA)
- Day 9 ARDS: Lobar collapse: prolong trendelenburg (PAC)
- Fi_{O2}:1; PEEP: 16; Crs: 27 mL/cmH_2O, V_T: 7.4 V_E: 11.8 L/m;
- Aeroprost 50 ng/kg/m;
- RM PC 45/25 x 3min
- Resulting ABG: 7.51/41/63 VD/VT = 0.60



Recruitment = Pressure x Time

- Dynamic process, variable time course.
- Time Required: ↑ Viscosity = ↑ time necessary to open sequentially collapsed airways & alveoli
- Paw needed to recruit collapsed small airways is determined by:
  - Viscosity, thickness, surface tension of the airway lining fluid,
  - airway radius,
  - axial wall traction exerted by the surrounding alveoli,
  - presence of surfactant.

Prone Positioning,PEEP, RM: Manifestation of CREEP!

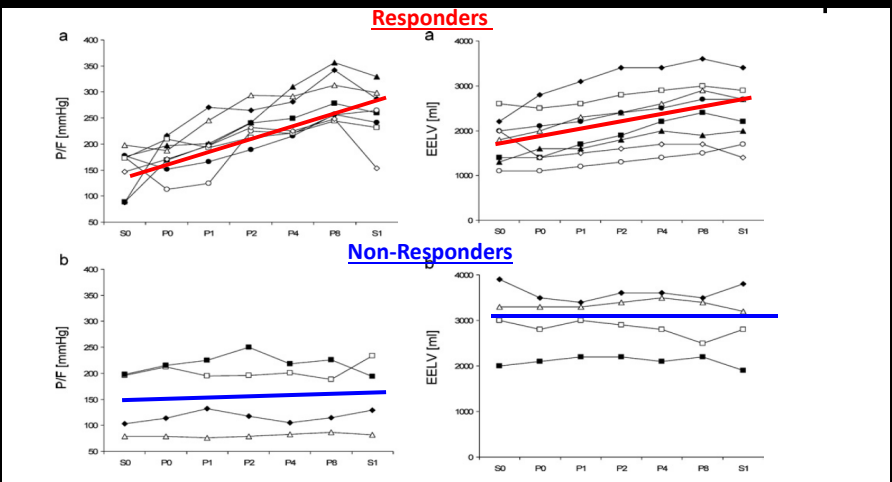
- Progressive ↑ in pulmonary volume occurring under constant airway pressure (lungs & chest wall).
- Viscoelastic property* of tissue that "yield" their shape over time under constant stress
- "Slow" gradual ↑ in Oxygenation

*think of the properties of caramel or drying glue

Van de Woestijne 1967, Respir Physiol

Increased PP Time Enhances Oxygenation

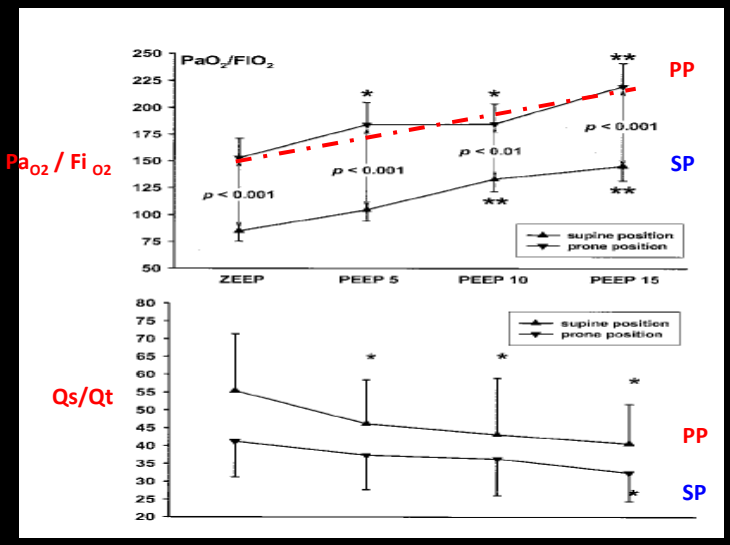
25% Early (≤ 4h); Late? No plateau in P/F after 8h



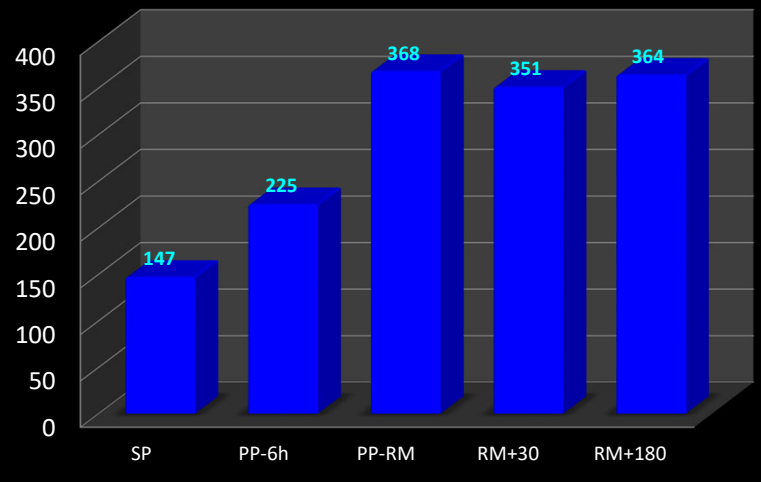
Reutershan Clin Sci 2006

PP Enhances Effectiveness of PEEP in ARDS

Grannier et al Intensive Care Med 2003



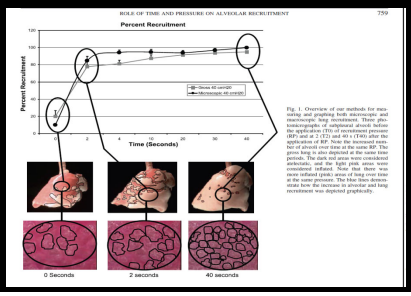
Effect of Adding RM to Prone Positioning on PaO2/FiO2 in ARDS



Oczenski Crit Care Med 2005

Why Inspir Time of 1.5-2 s Needed During an RM?

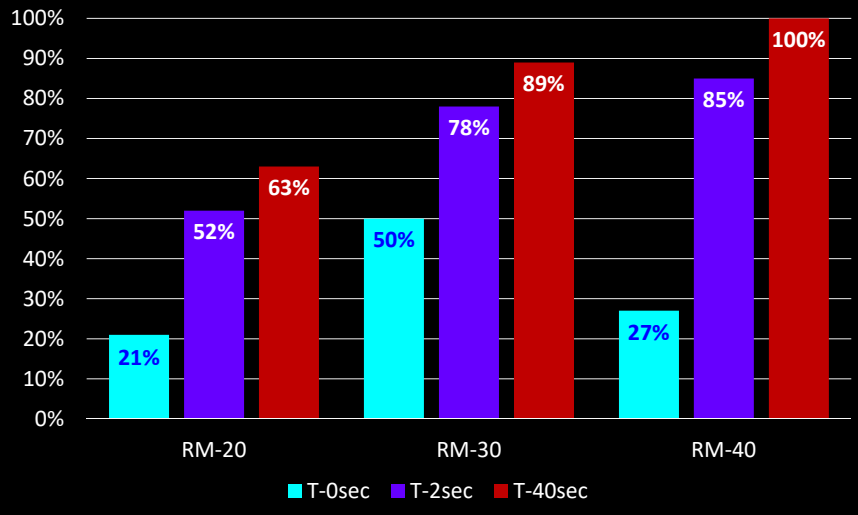
Mean Inspr Time Constant (Tau) was ~0.7sec.
~87% full recruitment might be achieved with TI of 1.4sec (Tau x2) and 95% (Tau x 3) in ~ 2 sec.
Using a set Rate of 20, I:E 1:1 (1.5 sec T_I) would likely provide sufficient recruitment per breath while limiting the degree of transient acidosis



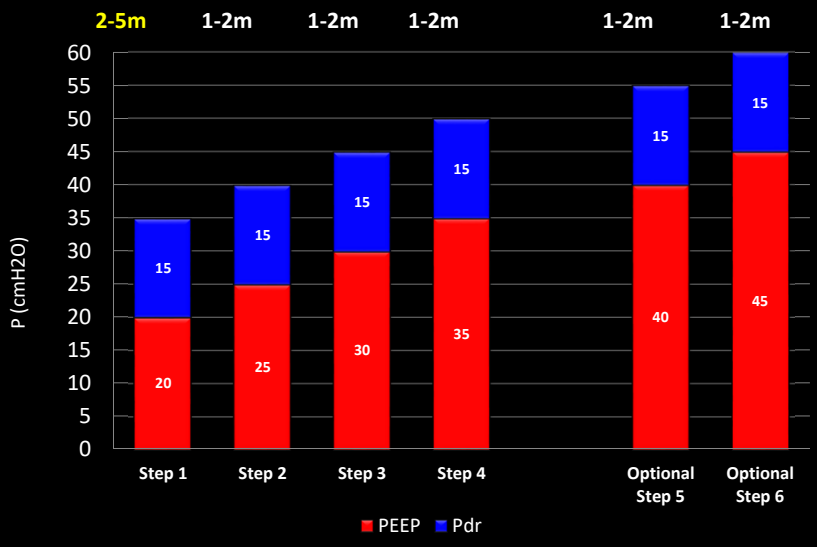
The role of time and pressure on alveolar recruitment

Scott P. Albert,[1] Joseph DiRocco,[1] Gilman B. Allen,[2,3] Jason H. T. Bates,[2,3] Ryan Lafollette,[1] Brian D. Kubiak,[1] John Fischer,[1] Sean Maroney,[1] and Gary F. Nieman[1]
[1]SUNY Upstate Medical University, Department of Surgery, Syracuse, New York; [2]Department of Medicine, Vermont Lung Center, University of Vermont, Burlington; and [3]Fletcher Allen Health Care, Burlington, Vermont

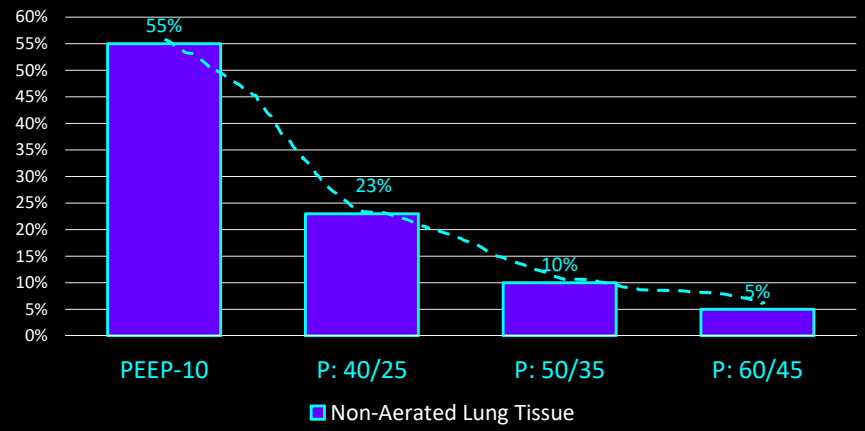
When RM Pressure is 40 cmH_2O: ~90% Alveolar Recruitment Achieved in 2 sec



ZSFGH Proposed Full Alveolar Recruitment for ARDS: Pdrive = 15 cmH_2O



Is it worth *initially* going above RM 50/35 cmH_2O in the Early ARDS?



How large is the lung recruitability in early acute respiratory distress syndrome: a prospective case series of patients monitored by computed tomography

Gustavo FJ de Matos[1], Fabiana Stanzani[1], Rogerio H Passos[1], Mauricio F Fontana[1], Renata Albaladejo[1], Raquel E Caserta[1], Durval CB Santos[2], João Batista Borges[3,4], Marcelo BP Amato[3] and Carmen SV Barbas[1,3*]

How High a Pplat is Needed to Recruit the Lungs in ARDS?

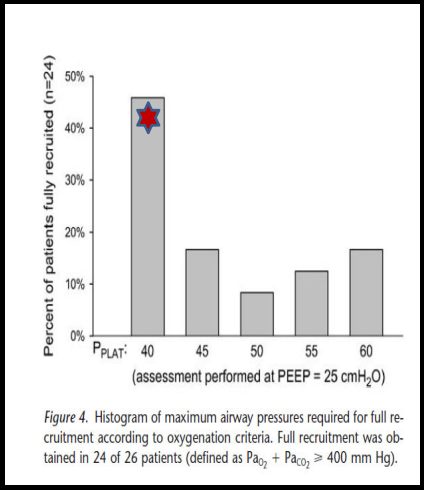


Figure 4. Histogram of maximum airway pressures required for full recruitment according to oxygenation criteria. Full recruitment was obtained in 24 of 26 patients (defined as $Pa_{O_2} + Pa_{CO_2} \geq 400$ mm Hg).

54% of all patients required a Pplat > 40 to reach full recruitment

~ 67% of patients recruit at a Pplat 40-50 cmH_2O (N = 15)

Reversibility of Lung Collapse and Hypoxemia in Early Acute Respiratory Distress Syndrome

João B. Borges, Valdelis N. Okamoto, Gustavo F. J. Matos, María P. R. Caramez, Paula R. Arantes, Fabio Barros, Ciro E. Souza, Josué A. Victorino, Robert M. Kacmarek, Carmen S. V. Barbas, Carlos R. R. Carvalho, and Marcelo B. P. Amato

Why RM is Needed: recruiting pressures follow a bimodal distribution of threshold opening pressure (TOP ≅ Pplat): Most ARDS patients readily achieve TOP of 20-30 cmH2O (PEEP 10-12, Pdr 12-15 w/ Vt 6 mL/kg; Crs ~35 mL/cmH_2O A minority require Pplat > 35 to begin recruitment

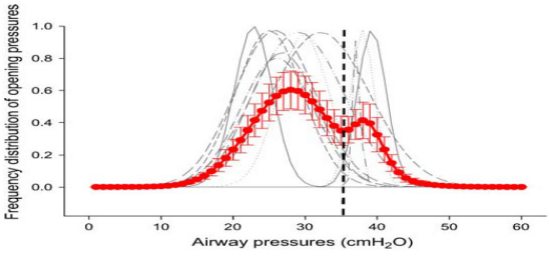


Figure 3. Frequency distribution of threshold opening pressures as a function of airway pressures. The distribution of opening pressures for individual patients is displayed in *gray* and the average distribution across patients in *red*. Calculations were performed according to Reference 55.

Implication: PEEP of 20 + Pplat 35 may not Cause sufficient recruitment to stabilize oxygenation → **Premature turn to ECMO?**

Reversibility of Lung Collapse and Hypoxemia in Early Acute Respiratory Distress Syndrome

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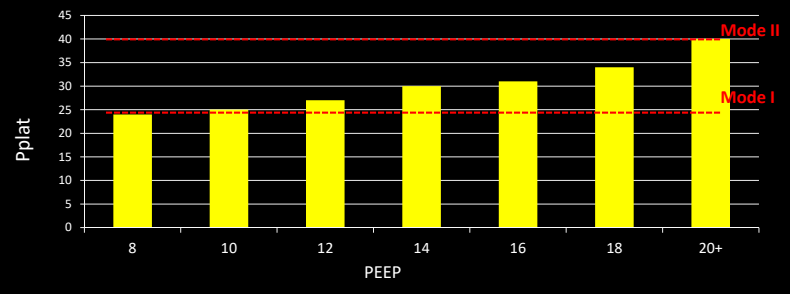
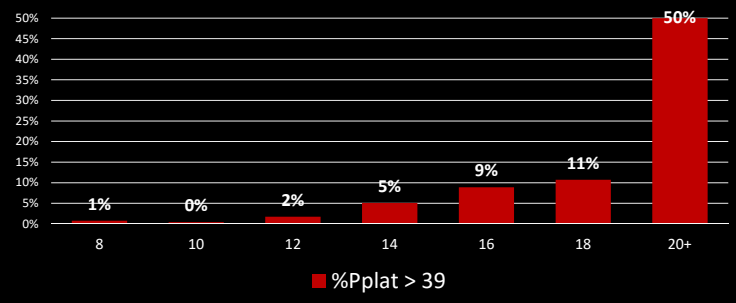
Lung Protection is at Odds with Recruitment (For each PEEP range the average Pplat and % of pts whose Pplat reached threshold for dorsal-caudal recruitment) SFGH ARDS Database





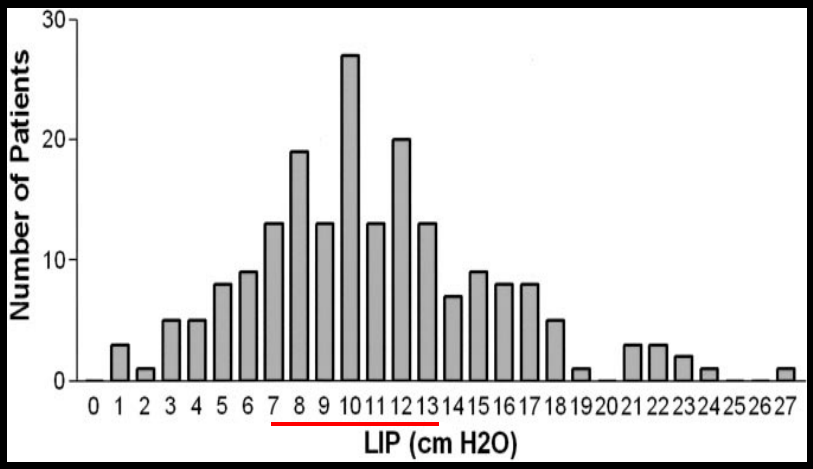
Effects of Inspiratory Pressure on Recruitment Varies According to Superimposed Pressure/Hydrostatic Pressure Gradient

- **Non Dependent Lung (~10%)**: No recruitment
- **Middle Lung (25%)** : recruitment ~ complete at Pplat 30 cmH_2O
- **Dependent Lung (~65% of tissues)** : recruitment continued up to maximum pressure studied: Pplat = 45 cmH_2O
- Transition phase Pplat 30 to 35 to 45 cmH_2O where non-aerated tissue noticably decreases

Recruitment and Derecruitment during Acute Respiratory Failure
A Clinical Study

STEFANIA CROTTI, DANIELE MASCHERONI, PIETRO CARONI, PAOLO PELOSI, GIULIO RONZONI, MICHELE MONDINO, JOHN J. MARINI, and LUCIANO GATTINONI

Moment of Zen: Who Needs Extraordinary Measures in ARDS? (hint most don't)



Set PEEP = LIP + 2-3 cmH_2O

Summary

- Only about 15-20% of patients need extraordinary therapies for ARDS (e.g. those whose oxygenation fails PEEP ~15)
- PP is lung-protective, usually improves oxygenation,unloads the right heart and ↓ mortality when P/F < 150
- ~ 50% lung tissue oriented towards the dorsum and when collapsed require Pcrit 40-60 cmH2O
- LPV (6 mL/kg) + 10-15 PEEP will not recruit the dorsal lung and reverse severe hypoxemia in these patients.
- Some combination of PP, higher PEEP (~14-20) and RM (40-50), inhaled vasodilators may be needed to stablize gas exchange
- Combination of these therapies provide enormous therapeutic flexibility to achieve prudent goals
- Pa_{O2}: 60-80 (that is stable) ; Fi_{O2}: $\leq$ .60; Pdrive $\leq$ 15 cmH_2O

CLOSING REMARKS AND POST TEST

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Friday, January 18, 2019 – 5:15 p.m. –5:20 p.m.