ADVANCES IN VENTILATOR MANAGEMENT OF ARDS

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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

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January 18, 2019

Conflict of Interest

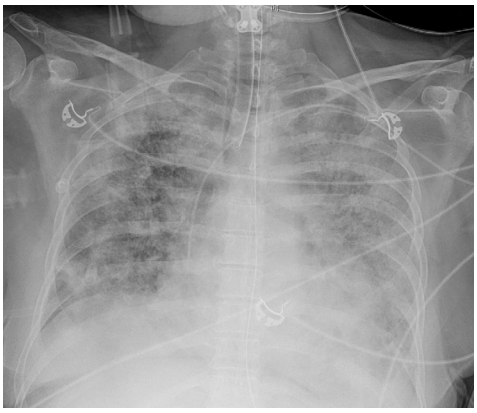
- I have no conflicts of interest

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

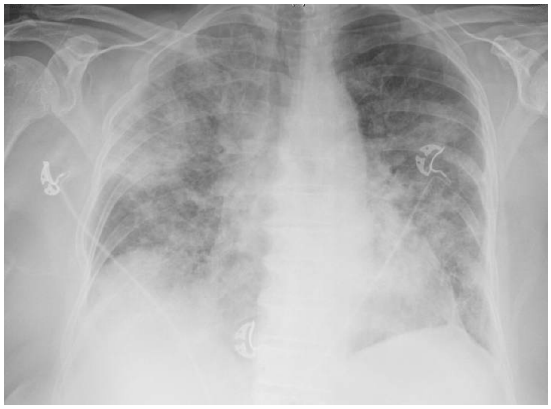
The Berlin Definition

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)

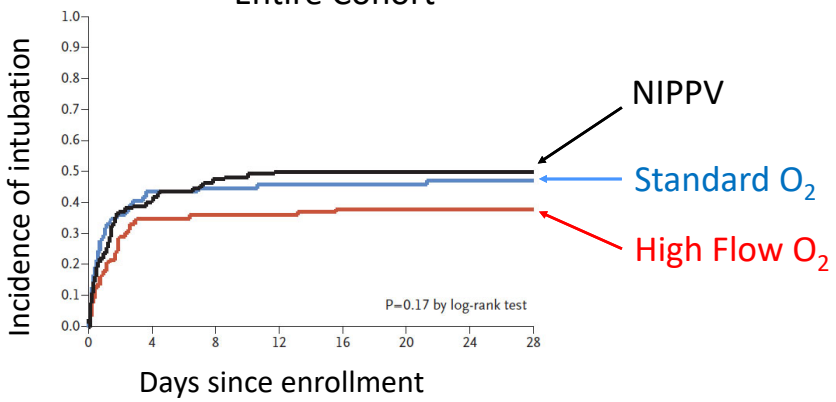
Noninvasive ventilation (N 110)

- 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

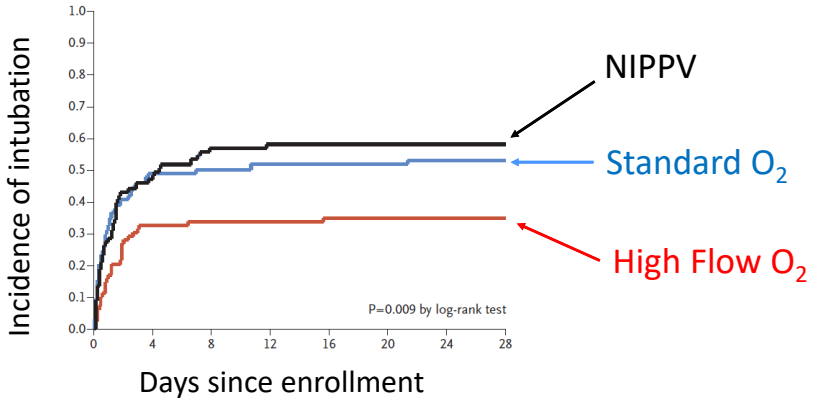
Entire Cohort



NEJM. 2015,372, 2185-2196

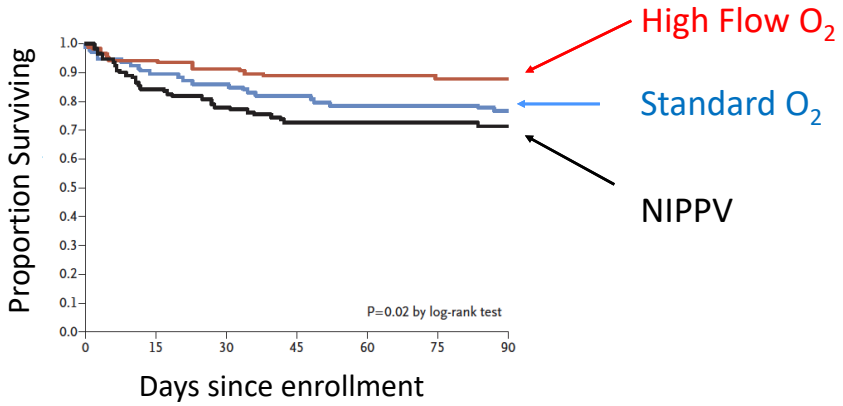
High flow for early HRF

Patients with P:F $\leq$ 200



NEJM. 2015,372, 2185-2196

High flow for early HRF

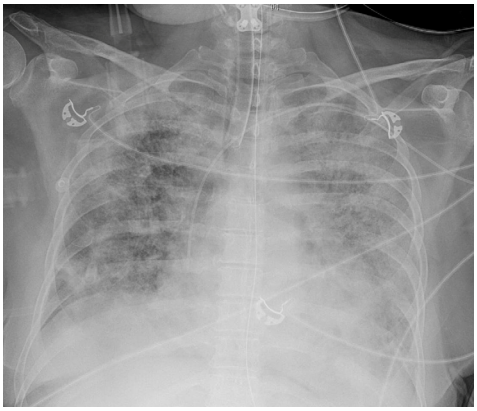


NEJM. 2015,372, 2185-2196

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

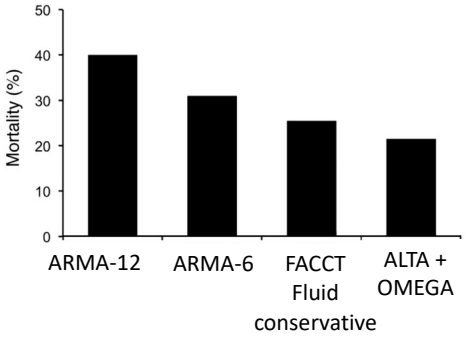
How good are we at implementing low tidal volume ventilation?: Lung Safe study in JAMA, 2016

- 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

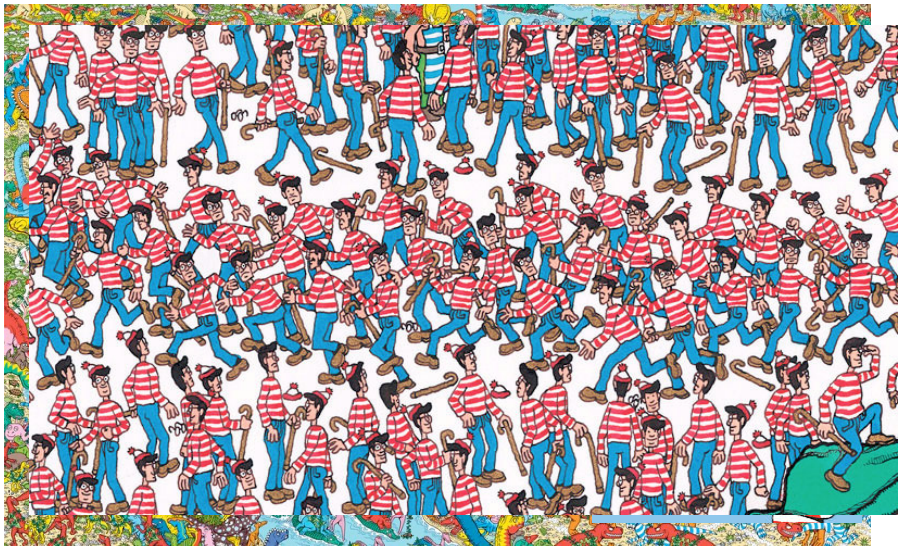
How good are we at implementing low tidal volume ventilation?: Lung Safe study in JAMA, 2016

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)

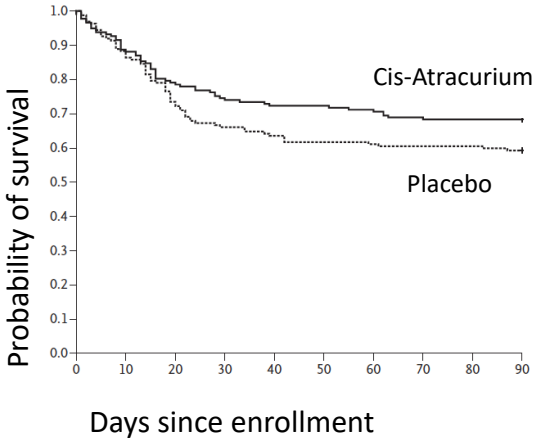
Neuromuscular blockade in ARDS

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

Lung protective ventilation

Probably*

Neuromuscular blockade (P:F<150)

* Probably = at least one multicenter RCT supports

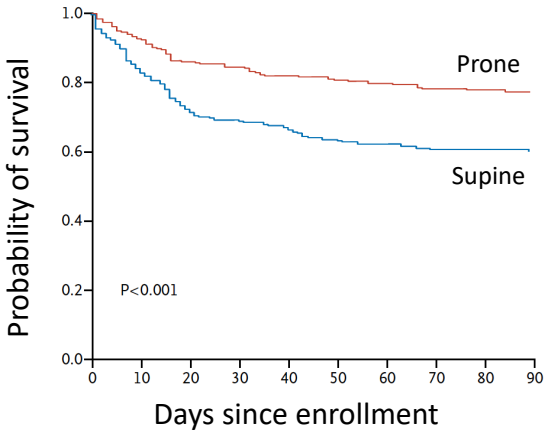
Prone positioning in severe ARDS

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

- Lung protective ventilation

Probably*

- 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

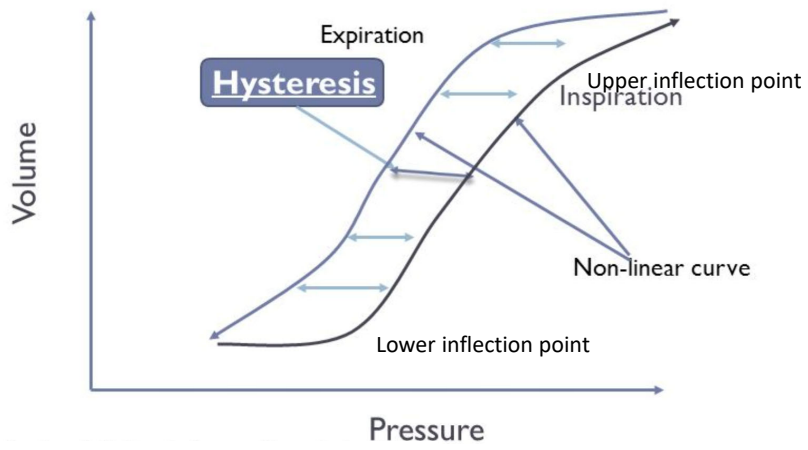
Maybe high PEEP helps some in ARDS

- 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?



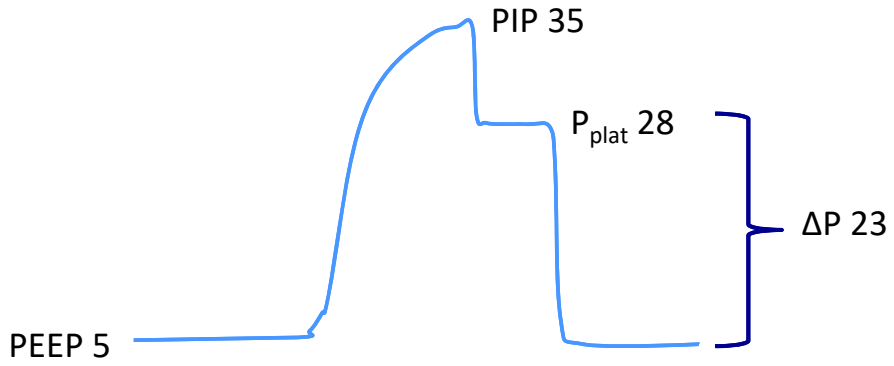
PEEP in ARDS: Does 1 size fit all?

Driving Pressure and Survival in the Acute Respiratory Distress Syndrome

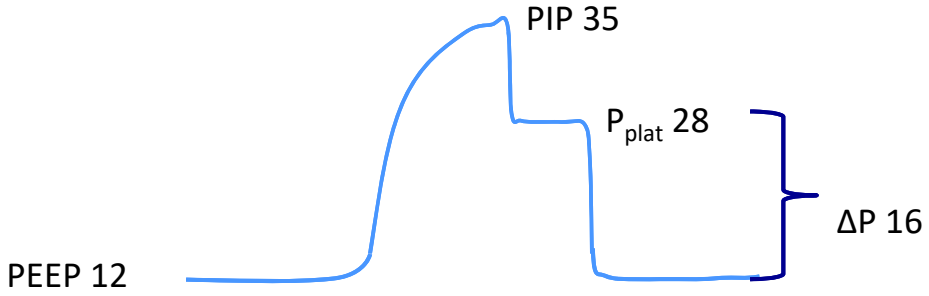
- 3562 patients in 9 RCTs of ARDS
- Is it volume or pressure that matters?
- Examined the driving pressure (ΔP)
  - $\Delta P = V_T/C_{RS}$
  - If no inspiratory effort $\Delta P = P_{plat}$-PEEP

NEJM. 2015, 372: 747-755

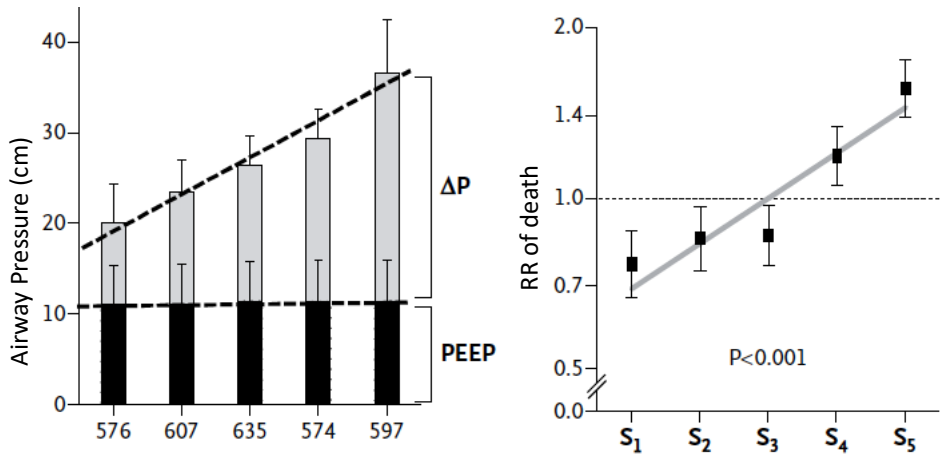
PEEP in ARDS: Does 1 size fit all?



PEEP in ARDS: Does 1 size fit all?

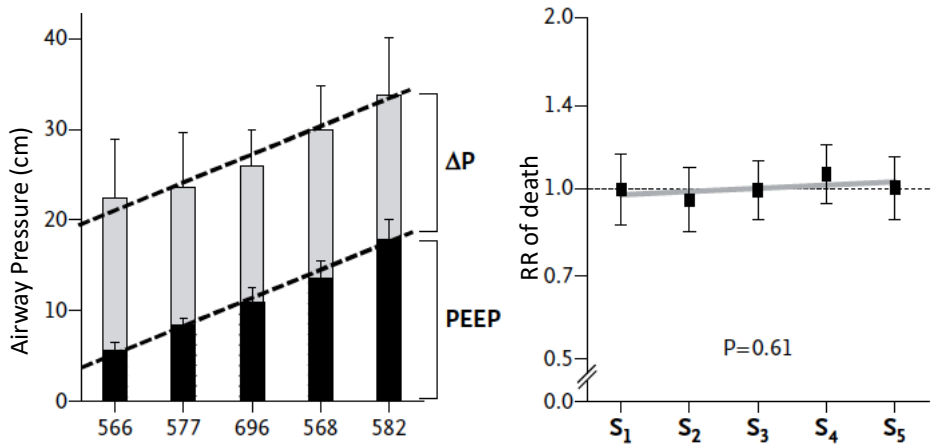


PEEP in ARDS: Does 1 size fit all?
Constant PEEP, changing P_{plat}



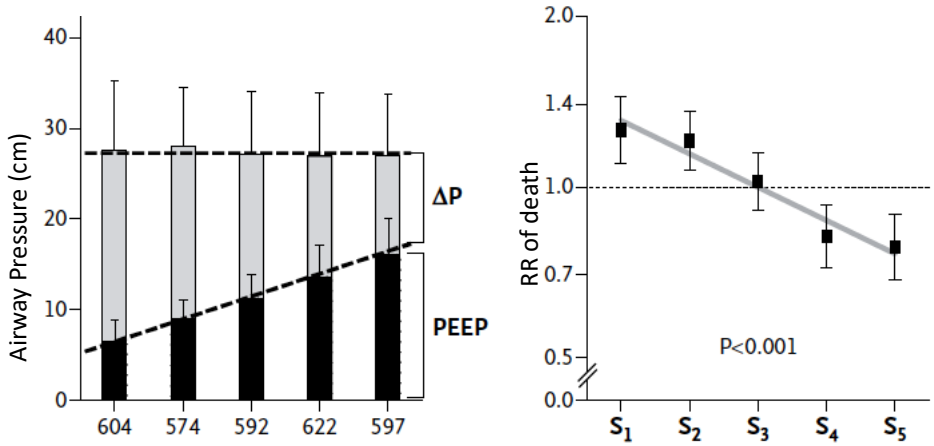
NEJM. 2015, 372: 747-755

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



NEJM. 2015, 372: 747-755

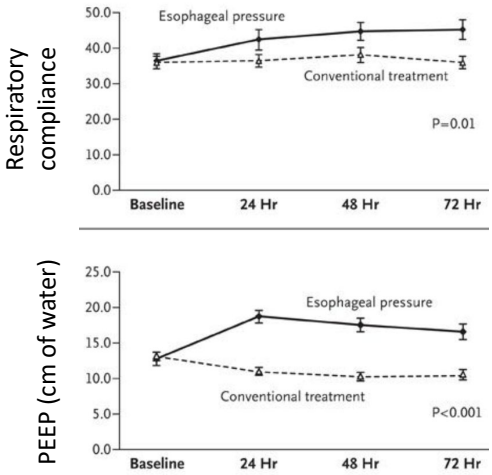
PEEP in ARDS: Does 1 size fit all? Constant Pplat, rising PEEP/falling Delta P



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

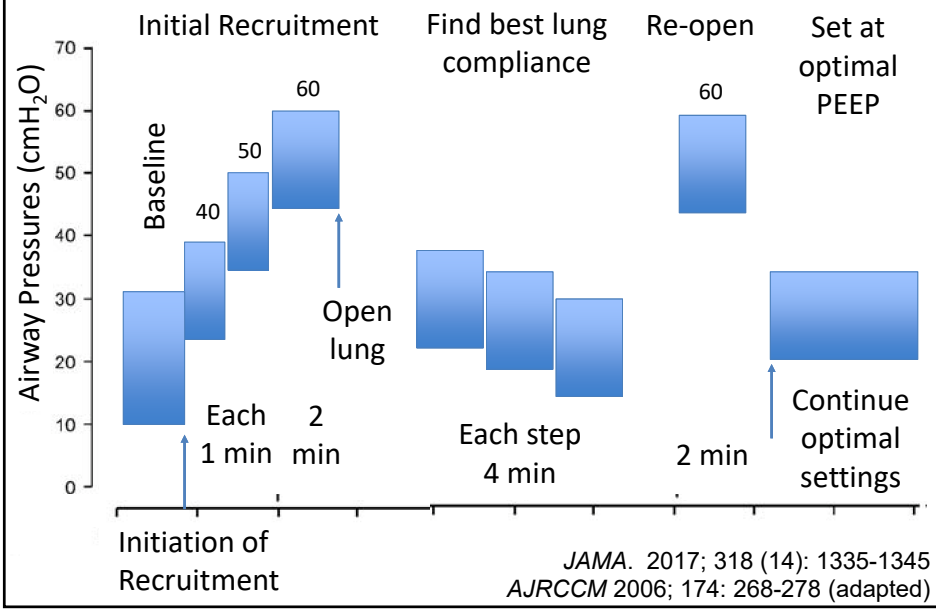
* Probably = at least one multicenter RCT supports

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

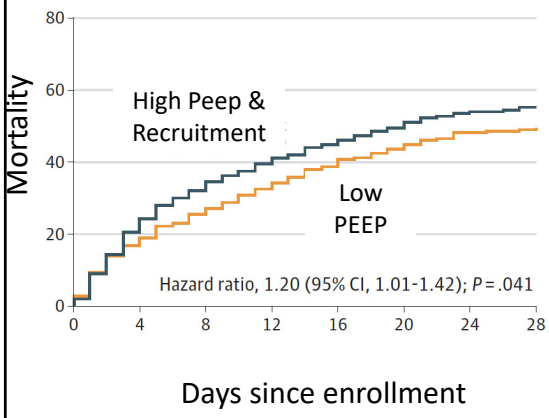


JAMA. 2017; 318 (14): 1335-1345
AJRCCM 2006; 174: 268-278 (adapted)

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?

Definitive	Probably*	No (partial list)
Lung protective ventilation	Neuromuscular blockade (P:F<150)	Recruitment Maneuvers
	Prone positioning (P:F<150)	Oscillatory Ventilation
	High or tai High or tailored PEEP	

* 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

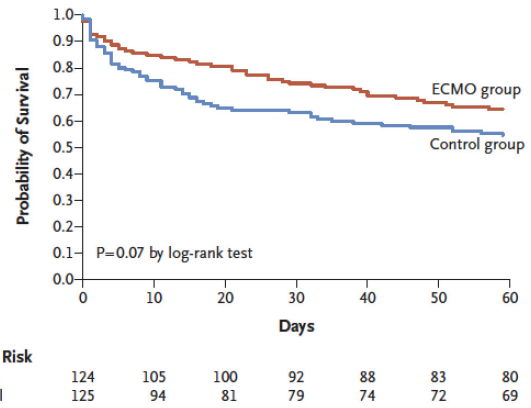


Figure 2. Kaplan–Meier Survival Estimates in the Intention-to-Treat Population during the First 60 Days of the Trial.

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?

Definitive	Probably*	No (partial list)
Lung protective ventilation	Neuromuscular blockade (P:F<150)	Recruitment Maneuvers
	Prone positioning (P:F<150)	Oscillatory Ventilation
	High or tailored PEEP	
	ECMO	

* 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