Acute Respiratory Distress Syndrome (ARDS)

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What is "Acute Respiratory Distress Syndrome"?

- Acute hypoxemic respiratory failure with diffuse, inflammatory lung injury leading to pulmonary vascular permeability edema
- Clinically, hallmark features are those of hypoxemia, bilateral radiographic opacities, with
  - increased shunt fraction
  - increased physiological dead space
  - and decreased lung compliance
- Pathologically, diffuse alveolar damage is most commonly noted

ARDS Definitions.. Then.. And Now..

AECC 1994 Definition	
Timing	Acute
Chest Imaging	Bilateral opacities on chest x-ray
Origin of Edema	Absence of left atrial hypertension
Oxygenation	ARDS →PaO_2/FiO_2 ratio less than 200
	Acute Lung Injury → PaO_2/FiO_2 ratio less than 300

ARDS Definitions.. Then.. And Now..

Berlin 2012 Definition			
Timing	Onset- Clarified " within 1 week of known clinical insult or new symptoms		
Chest Imaging (CXR or CT scan)	Bilateral opacities not fully explained by lobar consolidation, collapse or nodules		
Origin of Edema	Respiratory Failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g echocardiography) to exclude hydrostatic edema if no risk factor present		
Oxygenation	Mild	Moderate	Severe
	200<PaO_2/FiO_2 ≤ 300 CPAP or PEEP=> 5cms H_2O	100<PaO_2/FiO_2 ≤ 200 PEEP=> 5cms H_2O	PaO_2/FiO_2 ≤ 100 PEEP=> 5cms H_2O

Why is this important for us?

ARDS is fairly common and has high mortality

- 10% of all ICU patients and 23.4% of all patients with Mechanical Ventilation in ICU
- Overall hospital mortality- 40%
- ARDS Period Prevalence: Mild - 30%, Moderate - 46.6% and Severe -23.4% and hospital mortality progressively increases with severity to 46%
- ARDS can develop under our watch!

Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. JAMA. 2016 Feb 23;315(8):788-800. doi: 10.1001/jama.2016.0291.

How does ARDS develop?

- Direct Lung Injury
  - Pneumonia
  - Aspiration
  - Pulmonary contusion
  - Near-drowning
  - Inhalation injury
  - Reperfusion injury
  - Amniotic fluid and fat embolism
- Indirect Lung Injury
  - Sepsis
  - Massive trauma
  - Multiple transfusions
  - Acute pancreatitis

ARDS develops while in the hospital

First Hit, Second Hit Hypothesis

First Risk Modifiers

- Chronic Alcohol Use
- Smoking Status
- Low Albumin
- Acidosis
- Obesity
- Silent Aspiration

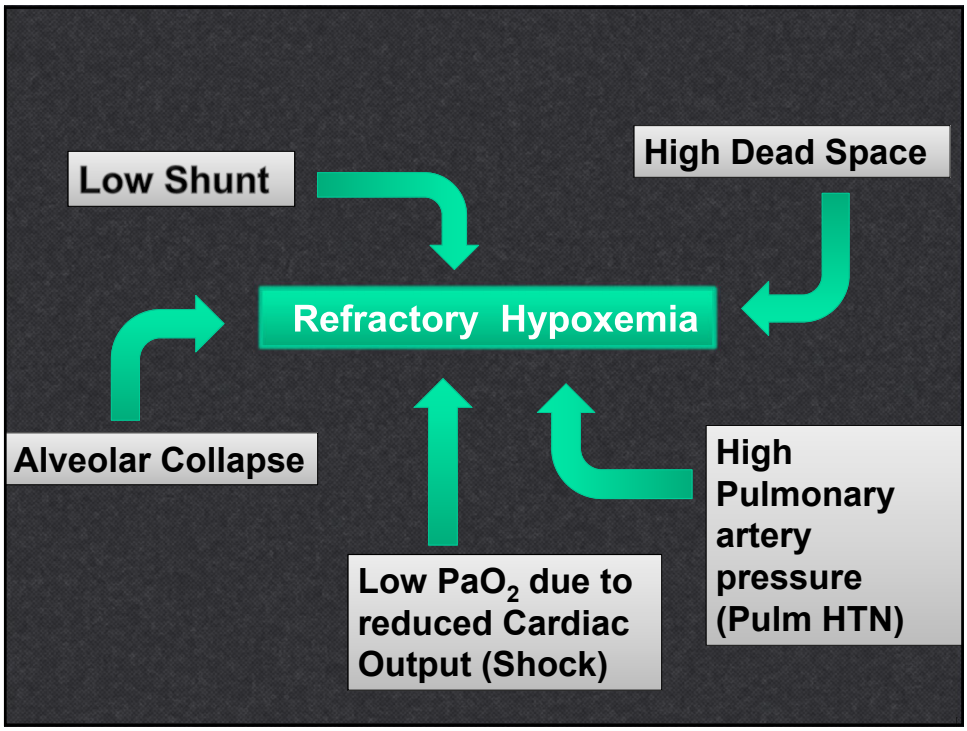
Second Risk Modifiers

- Ventilator Induced Lung Injury
- RBC, Platelets and FFP transfusions
- Fluid Overload
- FiO_2 use

Early identification of patients at risk of acute lung injury: evaluation of lung injury prediction score in a multicenter cohort study. Am J Respir Crit Care Med. 2011 Feb 15;183(4):462-70. doi: 10.1164/rccm.201004-0549OC.

Pathophysiological Changes and What They Mean..

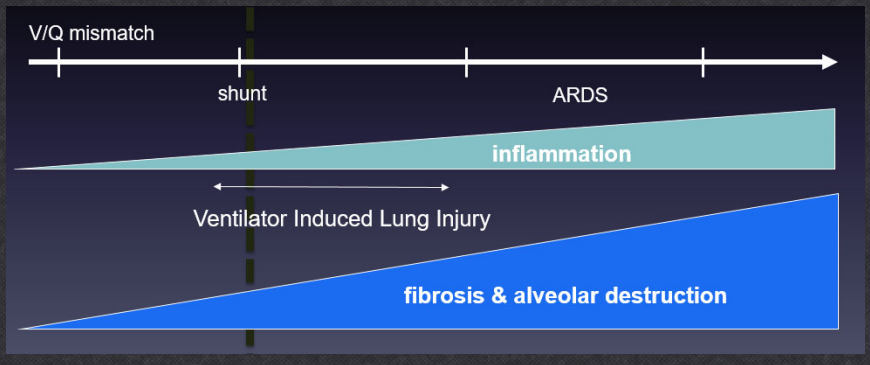
Acute Exudative Phase (Minutes to hours)	Pulmonary endothelial and alveolar epithelial injury→ permeability edema Surfactant dysfunction	Acute hypoxemia, Increased dead space Venous admixture (V/Q mismatch)
Chronic Proliferative Phase (5 – 7 days)	Maladaptive repair with mesenchymal cells and proliferative fibroblasts	Low compliance Pulmonary Hypertension Poor weaning and possibly tracheostomy Poor long term pulmonary function
Recovery	Alveolar edema and proteins are cleared, endothelial and epithelial injury repaired	Weaning and Ventilator Liberation



What can you do? What should you do?

First Step- RECOGNIZE ARDS! Start Lung Protective Ventilation!

- **Lung Safe - Only 60% patients with ARDS were diagnosed on day of admission**
- **The continuum of lung injury, like sepsis time probably matters here too!**



- VT: How to set a safe VT? Is a low VT good for all?
- PEEP: How should the appropriate PEEP be determined?
- Plateau pressures: keep limited , <30cms, what else do we need to know
- FiO_2: Yes, we know too much is bad, but how do we lower it when the patient needs oxygen?

Lung Protective Ventilation

Low Tidal Volume = Survival

Low (6ml/kg IBW) vs traditional tidal volume (12kg/IBW) in ARDS

- 6cc/kg tidal volume group had 8.8% absolute mortality benefit (NNT=12)
- Proportion alive and off ventilator improved
- Non-pulmonary organ failure improved
- Markers of inflammation reduced

ARDSNet. N Eng J Med 2000;342:1301-1308

CARING FOR THE CRITICALLY ILL PATIENT

Association Between Use of Lung-Protective Ventilation With Lower Tidal Volumes and Clinical Outcomes Among Patients Without Acute Respiratory Distress Syndrome

A Meta-analysis

JAMA, October 24/31, 2012—Vol 308, No. 16

- Eligible -lower vs higher Vt in patients without ARDS at onset of MV
- 20 studies, 2822 patients
- Randomized studies- 15 , non randomized studies- 5
- Decrease in ALI (RR- 0.33; 95% CI, 0.23 to 0.47; NNT- 11)
- Mortality (RR, 0.64; 95% CI, 0.46 to 0.89; NNT, 23)

Non-volume controlled mode is the most important barrier to implementation of Lung Protective Mechanical Ventilation

Risk factors for underuse of LPV in ALI

Table 2 Unadjusted and multivariable-adjusted predictors of not receiving LPV

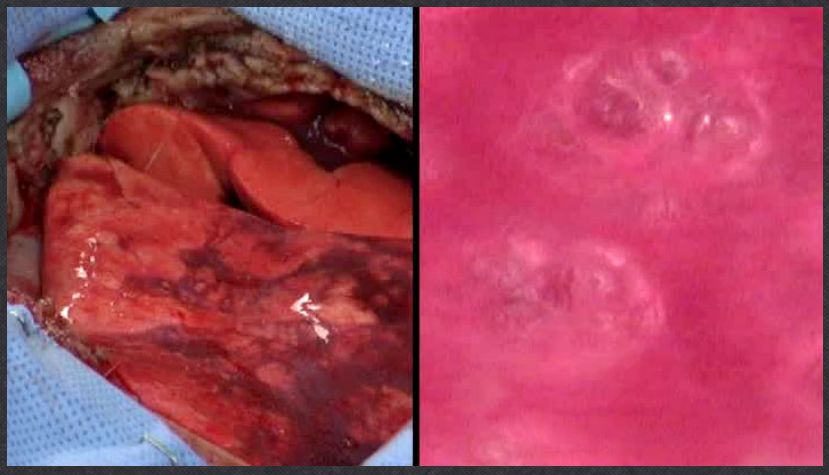
Variable	Unadjusted OR (95% CI), P	Adjusted OR (95% CI), P
Age, per SD (16 y)	1.14 (1.02-1.28), .024	1.18 (1.02-1.38), .028
Sex, female	2.03 (1.61-2.58), .0001	NS
Race, white vs nonwhite	1.26 (0.99-1.60), .059	1.40 (1.05-1.88), .023
BMI per SD (7.3 kg/m^2)	1.12 (0.99-1.26), .076	NS
Height, per SD (10 cm)	0.56 (0.50-0.64), .0001	0.55 (0.48-0.63), .0001
Weight, per SD (22 kg)	0.86 (0.77-0.97), .01	NS
SAPS II, per SD (14)	0.86 (0.77-0.97), .01	0.78 (0.67-0.92), .003
Direct lung injury	0.76 (0.59-0.98), .035	NS
Dialysis	3.80 (0.87-16.5), .075	NS
AIDS	0.64 (0.42-0.97), .036	NS
Radiographic lung injury score per SD (0.57)	0.84 (0.74-0.95), .005	0.83 (0.70-0.95), .009
Non–volume-control ventilator mode	3.18 (2.03-3.97), .0001	3.07 (1.78, 5.27), .0001
Serum bicarbonate per SD (5.5 mmol/L)	0.92 (0.82-1.03), .14	0.83 (0.71-0.97), .017
Duration of ICU stay before study enrollment per SD (2 d)	0.90 (0.80-1.01), .078	0.84 (0.73-0.98), .02

Hosmer-Lemeshow Goodness of fit for adjusted model P = .33, c-statistic 0.712. NS indicates not significant and not included in final adjusted model.

Walkey et al. J Crit Care Volume 27, Issue 3, June 2012

PEEP="STABILIZE ALVEOLI"

Prevent over distension and under recruitment



Video provided courtesy of Dr Christopher J. Farmer.

High or Low PEEP?

	Control group	Exp group	Findings
ALVEOLI[1]	6ml/kg and low PEEP	6ml/kg and high PEEP 80 pts recruitment maneuver	No difference in mortality
LOV[2]	6ml/kg and low PEEP	6 ml/kg and high PEEP Recruit if vent disconnect	
EXPRESS[3]	6ml/kg, mod PEEP	6 ml/kg and PEEP to target plateau (28-30)	

1. NEJM 2004;351:327-336
2. JAMA 2008;299:637-345
3. JAMA 2008;299:646-655

What else helps to set PEEP?

Think About…

Driving Pressure as a Ventilator Variable

Strong association between ΔP and survival even lung-protective ventilator settings (relative risk of death, 1.36; CI 95%, 1.17 to 1.58; P<0.001)

Mechanical ventilation guided by **esophageal** pressure in acute lung injury. **Talmor** D, Sarge T, Malhotra A, O'Donnell CR, Ritz R, Lisbon A, Novack V, Loring SH.N Engl J Med. 2008 Nov 13;359(20):2095-104

Transpulmonary Pressure

A ventilator strategy using esophageal pressures to estimate the transpulmonary pressure significantly improves oxygenation and compliance

Mechanical ventilation guided by **esophageal** pressure in acute lung injury. **Talmor** D, N Engl J Med. 2008 Nov 13;359(20):2095-104. doi: 10.1056/NEJMoa0708638.

How to set Optimal PEEP

- Recruitment potential - most important
- PEEP of zero (ZEEP) harmful in ARDS
- Usually 8-15 cm appropriate (up to 18 cms in studies), PEEP> 24 cms seldom required
- Driving Pressure: PEEP- Plateau pressure, aim for less than 15
- Transpulmonary pressure and chest wall mechanics play an important role
- Limiting factors- No recruitment, worsening hemodynamic compromise or hypotension

Plateau Pressure – End Inspiratory Alveolar Pressure

- Inspiratory pause of at least 0.5 sec needed to measure plateau pressure
- Surrogate for maximum lung distension, per ARDSnet Data: Suggestions to limit to 25-30cms
- Intra thoracic pressures can be high due extrinsic factors such as obesity, pleural effusion, abdominal distension etc..
- In these conditions, plateau pressure correlates poorly with the transpulmonary pressure
- If plat pressure> 30 cms then
  - Increase sedation, may require neuromuscular blockade
  - Drop TV to 4cms
  - May have to reduce PEEP by 2 cm decrements

Setting the Ventilator in ARDS for Lung Protective Ventilation

- Prefer Volume Control Mode
- V_T = 6 ml/kg IBW
  - May adjust as low as 4 ml/kg IBW as needed or upto 8ml/kg IBW
- Set RR, Permissive Hypercapnia acceptable
  - Arterial pH as low as 7.20- 7.15 due to hypercapnia may be accepted
- Set PEEP: ARDSnet PEEP-FiO_2 tables, Driving Pressure

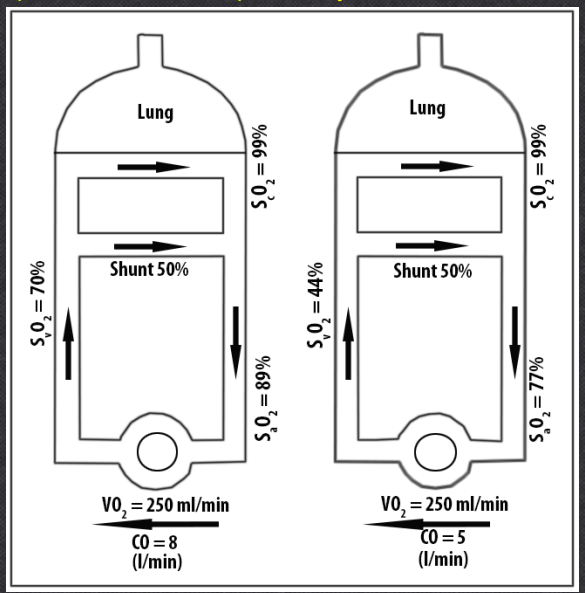
Setting the Ventilator in ARDS for Lung Protective Ventilation

- **Measure Plateau Pressure**, aim to limit less than 30 cm H_2O
- **Pay attention to patient size and chest wall**
- **Prevent patient ventilator dysynchrony**
  - NMB, heavy sedation
- **Adjust FiO_2 to target:**
  - PaO2 55-80 mmHg
  - SpO2 88-95%

"IDENTIFY SHOCK"

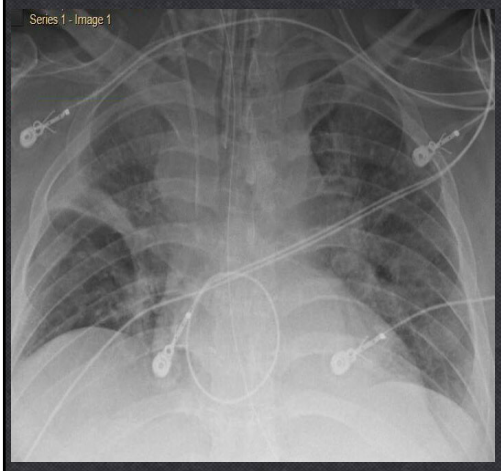
- Hemodynamic instability with shock may be common with initial ARDS presentation with sepsis
- Early optimization of cardiac output is essential to improve hypoxemia

Effect of cardiac output (CO) on mixed oxygen saturation (SvO2) and arterial oxygen saturation (SaO2) in patients with an intrapulmonary shunt of 50%



Curr Opin Crit Care. 2011 Feb;17(1):50-6. doi: 10.1097/MCC.0b013e3283427280.

What change would you make on the ventilator next?

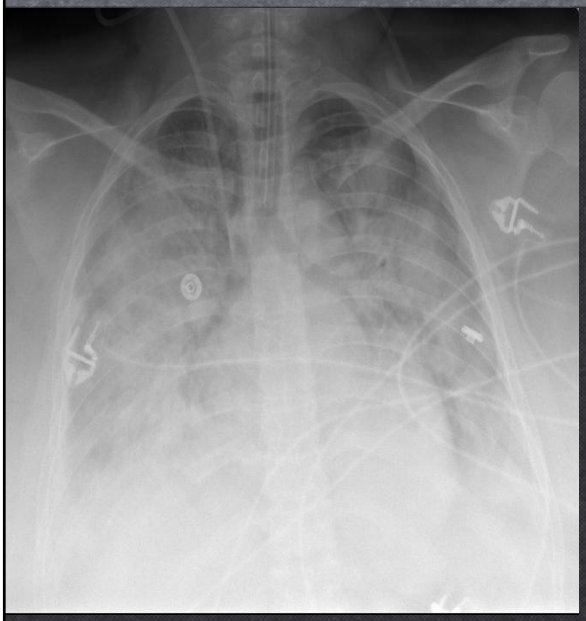


- 40yo with gram negative bacteremia
- On vasopressors Worsening oxygenation
- ABG pH:7.32 PaCO2:33 PaO2=55
- MV mode: A/C
- RR: 32 per min
- Tidal Volume: 500cc (7 ml/kg)
- PEEP 6; FiO2 100%

What change would you make on the ventilator next?

- 65yo intubated for airway protection with drug overdose
- ABG pH:7.38 $PaCO_2$:44 PaO_2=110
- MV mode: A/C
- RR: 18 per min
- Tidal Volume: 600cc (9 ml/kg)
- PEEP 6; FiO_2 50%

What would you do next?



- 35 yo F, Day 2- post partum with acute onset dyspnea
- Ventilator settings:
  - FiO_2 100%,
  - Peep 18 cms
  - TV: 320 (5cc/kg IBW)
  - RR 28,
  - Plateau pressure 28
- PaO_2/FiO_2 ratio : 57
- ABG: pH=7.20 $PaCO_2$ = 63 PaO_2= 57, bicarb: 21
- Transthoracic Echo: Acute RV failure, LV preserved
- Increasing vasopressor requirements

Source: MFMER

What next!

So you did all this, but the patient does not respond.

Life Saving Therapy In ARDS

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ARDS Care 2018

- ARDS care is NOT just supportive care
- There are active measures we can take today to save lives
- We've got to look for the patients that we can help
  - They are usually NOT the hardest to ventilate
- What can we do?

Helps Oxygenation / Ventilation

- High PEEP
- Diuretics
- Inhaled Vasodilators

Diuresis
A Dry Lung is a Happy Lung

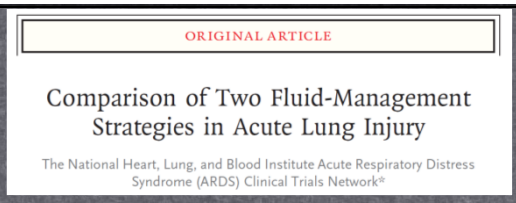
- Starling's Law and Pulmonary Edema
- $Q_f = K_{fc}\,[(P_{mv} - P_i) - (s_d)(TT_{mv} - TT_i)]$
- Where
  - Q_f = net fluid filtration
  - K_{fc} = capillary permeability coefficient
  - P = hydrostatic pressure
  - TT = osmotic pressure
  - mv = microvascular
  - i = interstitial
  - Sd = average osmotic coefficient

Diuresis
A Dry Lung is a Happy Lung

Increased in ARDS due to leaky capillaries

- $Q_f = K_{fc} [(P_{mv} – P_i) – (s_d)(TT_{mv} – TT_i)]$

Increased in ARDS due to volume overload
Diuresis should help here



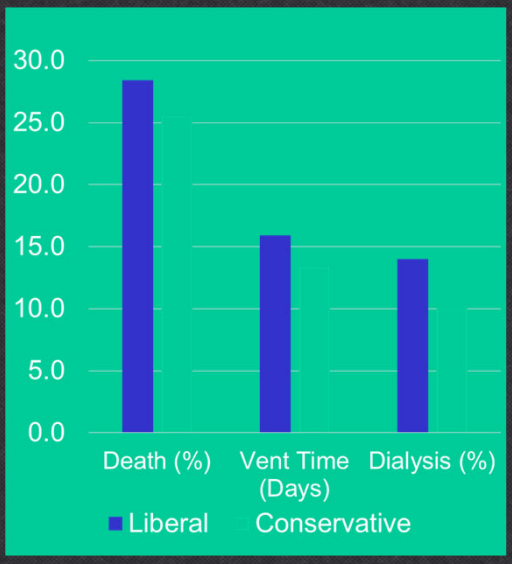
ORIGINAL ARTICLE

Comparison of Two Fluid-Management Strategies in Acute Lung Injury

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

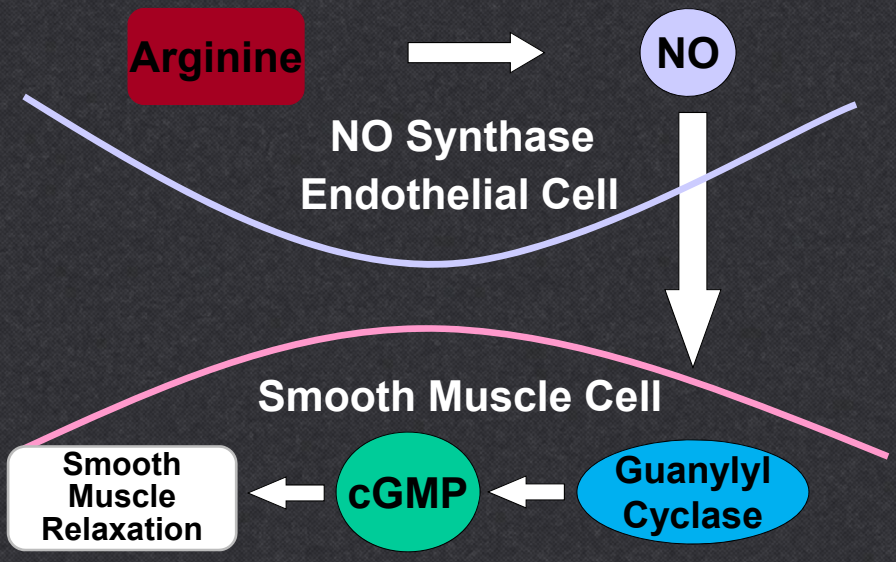
- 1001 patients with ARDS
- Randomized to “liberal” versus “conservative” fluid management
- Liberal targeted CVP 10-14mmHg
- Conservative CVP 4-8mmHg

Diuresis to Get Off Vent

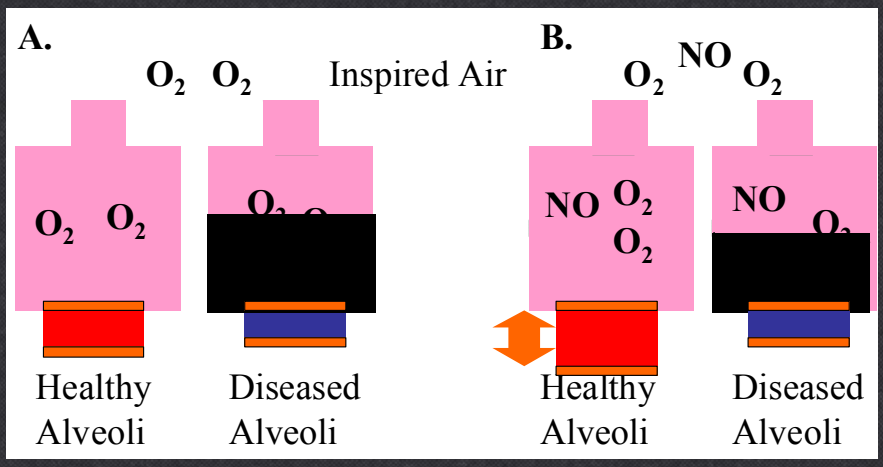


- IF
  - No shock
  - Good urine output
  - "Wet" (CVP > 4)
  - DIURESIS
- Averaged 2.5 less days on vent

Inhaled Vasodilators



Mechanism Inhaled NO



Inhaled Vasodilators and ARDS

- What has been shown:
  - Decreased Pulmonary Vascular Resistance (PVR)
  - Decreased Pulmonary Arterial Pressure (PAP)
  - Decreased Shunt Fraction and V/Q mismatch
  - Improved SaO_2
- What has not been shown:
  - Improved mortality
  - Sustained improvement in oxygenation
  - Increased time off vent
  - Decrease ICU or hospital days

Benzing et al, '94; Rossaint, '93

Improves Mortality

- Prone Ventilation
- Extracorporal Membrane Oxygenation (ECMO)
- Airway Pressure Release Ventilation (APRV)
- Sedation Interruption
- Paralysis
- Low Tidal Volume

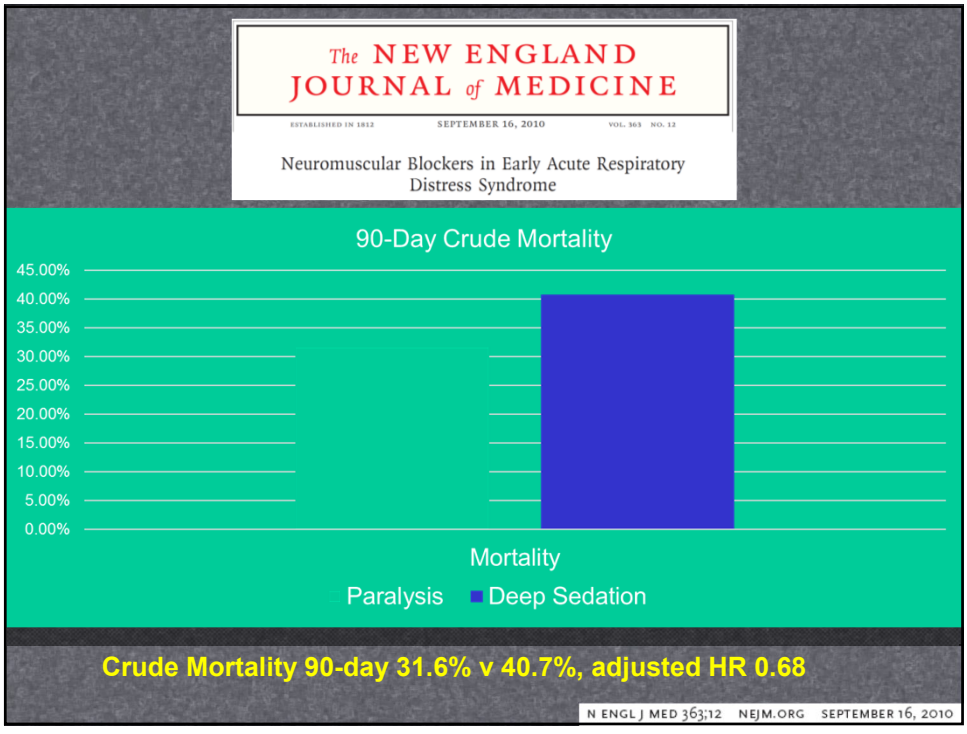
Which of These Saves Most Lives?
Number Needed to Treat (NNT)

- Low Tidal Volume NNT 10
- Paralysis NNT 9
- Sedation Interruption NNT 7
- APRV NNT 7*** (small study)
- ECMO NNT 5-8
- Prone Ventilation NNT 6

So You Want MORE Sedation Paralytics in ARDS

- Often used to improve compliance and reduce oxygen consumption
- In 340 patients with P/F ratio < 150
- Assigned to 48h of deep sedation (Ramsay 6) and either cisatracurium or placebo

N ENGL J MED 363;12 NEJM.ORG SEPTEMBER 16, 2010



Crude Mortality 90-day 31.6% v 40.7%, adjusted HR 0.68

N ENGL J MED 363;12 NEJM.ORG SEPTEMBER 16, 2010

What About Sedation?

- Sedation is often necessary for ventilator compliance and patient comfort
- However, sedation should be considered a necessary evil
- Many studies have demonstrated sedation protocols improve outcomes, for example….

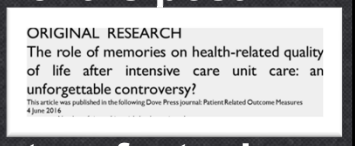

Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial

Timothy D Girard, John P Kress, Barry D Fuchs, Jason W W Thomason, William D Schweickert, Brenda T Pun, Darren B Taichman, Jan G Dunn, Anne S Pohlman, Paul A Kinniry, James C Jackson, Angelo E Canonico, Richard W Light, Ayumi K Shintani, Jennifer L Thompson, Sharon M Gordon, Jesse B Hall, Robert S Dittus, Gordon R Bernard, E Wesley Ely

- 336 Patients compared between usual care and paired sedation interruption with spontaneous breathing trial
- 1-year mortality
  - 44% (intervention) v. 58% in control
  - NNT 7
- More self-extubations in intervention group, but reintubation rates the same

Do My Patients Want to Remember This?

- Patients without memories of the ICU were more likely to report lower health-related quality of life at 6-months post-ICU stay


ORIGINAL RESEARCH
The role of memories on health-related quality of life after intensive care unit care: an unforgettable controversy?
This article was published in the following Dove Press journal: Patient Related Outcome Measures
4 June 2016

- Patients with delusions, but no factual memory of the ICU had higher incidence of PTSD at 8 weeks


Memory, delusions, and the development of acute posttraumatic stress disorder-related symptoms after intensive care

Christina Jones, Mphil; Richard D. Griffiths, MD, FRCP; Gerry Humphris, PhD, M Clin Psych; Paul M. Skirrow, BSc

When the RT Talks Fancy! Airway Pres Release (APRV)

- Ventilator mode where patient spends majority of the time at high PEEP with intermittent brief "release" times to allow for ventilation
- Patients are able to spontaneously breath while at high PEEP
- In theory, higher PEEP and spontaneous breathing facilitate open lung ventilation and lower sedation needs

Does APRV Work?

- No evidence it's better (or worse)
- Danger with large transpulmonary pressure and large "release" volume
- In one small study, APRV patients had
  - ✓ More time off vent
  - ✓ Improved survival
  - ✓ Decreased sedation
- More work is needed to confirm role in ARDS and develop protocols

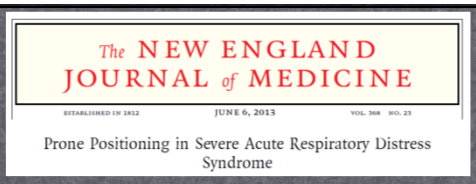
Extracorporeal Membrane Oxygenation (ECMO)

- 180 adults with severe ARDS
- Randomized to transfer to ECMO-capable center vs. Usual Care (at original hospital)
- 25% of "ECMO" patients did not placed on ECMO
- 6-month mortality
  - ✓ ECMO 37% versus Usual Care 53%
- ECMO can save lives, but
  - ✓ Need to be careful about patient selection
  - ✓ More important to be ECMO capable than get everyone on ECMO

Lancet 2009:374:1351

Easy, Cheap, Fast Proning in ARDS

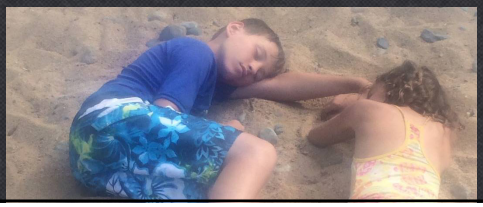
- Proning
  - ✓ Laying patient on stomach for much of the day (> 16-hours)
- Improves pressure distribution
  - – Less vent associated lung injury
- Improves secretion drainage
- Improves ventilation profusion matching → ventilation and oxygenation improve



- 237 patients with ARDS
- P/F ratio 150 (moderate to severe)
  - ✓ e.g. PaO_2 of 74mmHg on 50% FiO_2
- Proned AT LEAST 16-hours a day
- Mortality 23.6% vs. 41%

Proning for ARDS
Not for Rescue Anymore

- Proning is FREE!
- Proning can be done safely, just takes coordination with nursing, physicians, and respiratory therapists
- NNT for proning is 6
- Proning is not uncomfortable



What's the Future?

PETAL NETWORK
Prevention & Early Treatment of Acute Lung Injury

- Paralysis (again) - ROSE
- Vitamin D - VIOLET
- Fluids (again) – CLOVERS
- Non-PETAL Network Studies
  - ✓ Vitamin C for Septic ARDS
  - ✓ Mesenchymal Stem Cell Infusions

ARDS LIVE SAVING THERAPIES

What Buys Us Time

- PEEP
- Diuresis
- Inhaled vasodilators

What Saves Lives!

- Low Tidal Volume
- Minimize Sedation
- Paralytics
- Prone Ventilation
- ECMO
- APRV (maybe)