Breathing life into new therapies: Updates on treatment for severe respiratory failure

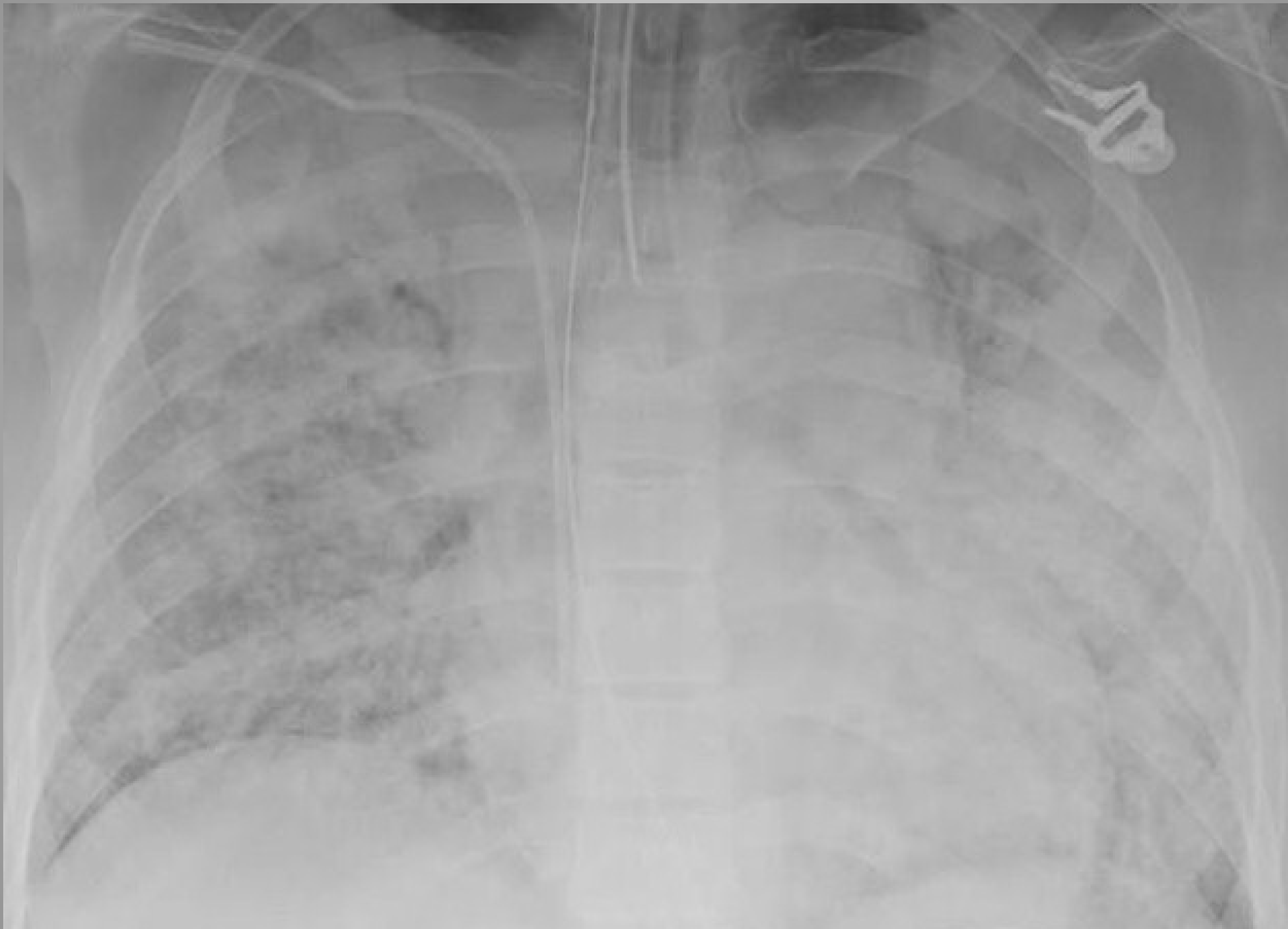
Whitney Gannon, MSN ACNP-BC

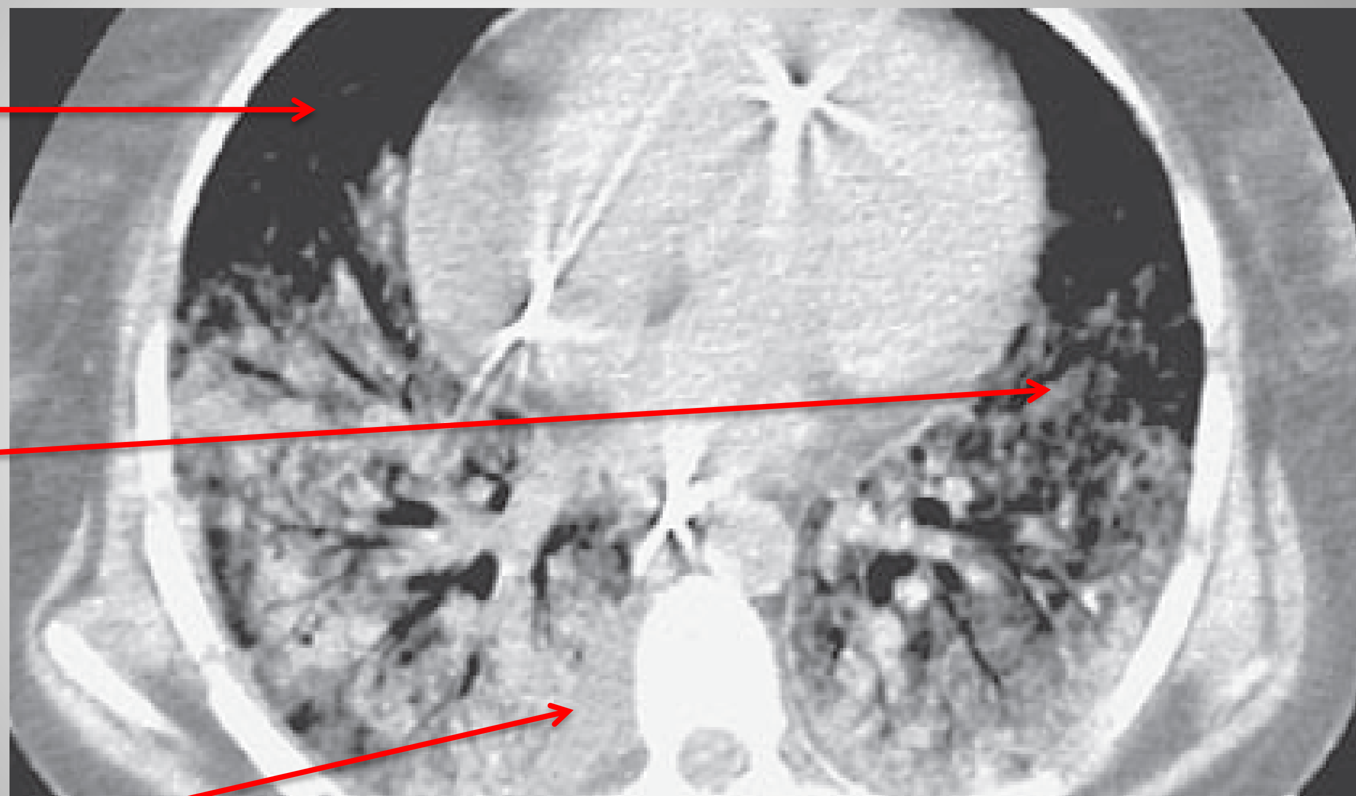
Overview

- Definition of ARDS
- Clinical signs and symptoms
- Causes
- Pathophysiology
- Management and updated treatments
  - Mechanical Ventilation
  - Supportive care
  - Refractory hypoxemia
- Prognosis
- Questions?

Definition of ARDS

- AECC definition 1994
- **Updated: The Berlin definition 2011**
  - Timing
    - Within 1 week of a known clinical insult or new or worsening respiratory symptoms
  - Chest imaging
    - Bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules
  - Origin of edema
    - Respiratory failure not fully explained by cardiac failure or fluid overload
  - Oxygenation
    - Mild: 200mmHg < Pa02/Fi02 </= 300mmHg with PEEP or CPAP >/= 5cm H20
    - Moderate: 100mg < Pa02/Fi02 </= 200mmHG with PEEP >/= 5cm H20
    - Severe: Pa02/Fi02 </= 100mmHg with PEEP >/= 5




Normal alveoli
Injured alveoli
Damaged alveoli

Clinical Signs and Symptoms

- Respiratory distress
  - Tachypnea
  - Tachycardia
  - Diaphoresis
  - Use of accessory muscles
- Cyanosis
- Diffuse crackles
- Cough
- Chest pain
- Hypoxemia

Causes of ARDS

- Infection
  - Sepsis
  - Diffuse pulmonary infections: Viral, Mycoplasma, PCP
  - Gastric aspiration
- Phyisical Injury
  - Mechanical trauma, head injury
  - Near-drowning
  - Fracture with fat embolism
  - Burns
- Inhaled Irritants
  - Oxygen toxicity
  - Smoke
  - Irritant gases and chemicals
- Chemical Injury
  - Heroin or methadone overdose
  - Acetylsalicylic acid
  - Barbituate overdose
  - Paraquat (inhaled vs. ingested or skin
- Hematologic conditions
  - Transfusions (TRALI), massive transfusion
  - Disseminated intravascular coagulation
- Pancreatitis
- Uremia
- Cardiopulmonary bypass
- Reperfusion injury after transplant
- Hypersensitivity reactions
  - Organic solvents
  - Drugs

Pathophysiology: Injury

- Healthy lungs vs. injured lungs
- Injury releases pro-inflammatory cytokines (e.g. TNF, IL-8) that recruit neutrophils to the lungs
- Neutrophils activated and release toxic mediators (e.g. reactive oxygen species, proteases)
- Causes further damage of capillary endothelium leading to pulmonary edema
- Alveolar injury produces diffuse alveolar damage

Pathophysiology: Consequences

- Impaired gas exchange
  - V/Q mismatch
  - Increased dead space
- Decreased compliance
  - Stiff, poorly or non-aerated lung
  - Fluid filled lung
  - Needs increased pressure to deliver Vt
- Increased pulmonary arterial pressure
  - Occurs in ~25% of ARDS patients
  - Hypoxic vasoconstriction
  - Can result in RV failure

Pathophysiology: Stages

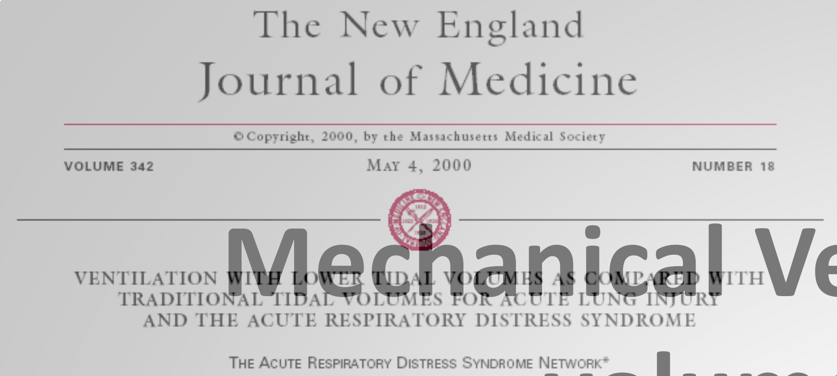
- Diffuse Alveolar Damage
- Acute exudative phase (7-14 days)
  - Hyaline membranes
  - Necrosis of alveolar epithelial cells
  - Endothelial injury and microvascular clotting
- Proliferative and fibrotic phase
  - Mixed cellular infiltrate leading to potentially reversible fibrosis

Management of ARDS

- Mechanical Ventilation
  - Low tidal volume
  - PEEP
  - ARDSnet protocol
- Supportive therapy
  - Fluid Management
  - Sedation
  - Paralysis
  - Other
- Refractory hypoxemia
  - Inhaled vasodilators
  - Prone Positioning
  - Extracorporeal Membrane Oxygenation
  - High Frequency Oscillatory Ventilation

Mechanical Ventilation

- Low tidal volume ventilation
  - Minimize alveolar over distention
  - Minimize plateau pressures
  - ARMA trial
- Open lung ventilation
  - Minimize cyclic atelectasis
  - Combines LTVV and PEEP to maximize alveolar recruitment
  - Risk of barotrauma given increased plateau pressures
- Mode
  - Volume or pressure limited
- Acute Respiratory Distress Syndrome Network (ARDSnet)
  - Clinical network to carry out multiple clinical trials
  - Goal to improve care of patients with ARDS


The New England
Journal of Medicine

© Copyright, 2000, by the Massachusetts Medical Society

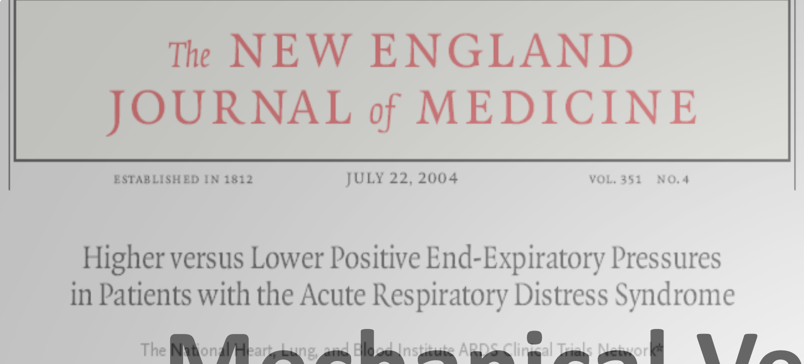
VOLUME 342 MAY 4, 2000 NUMBER 18

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*

Mechanical Ventilation: Low tidal volume ventilation

- Randomly assigned 861 mechanically ventilated patients with ARDS to receive LTVV (6mL/kg PBW) or conventional mechanical ventilation (12mL/kg PBW)
- Conclusion: mechanical ventilation with a lower tidal volume results in decreased mortality (31% vs. 40%) and increased ventilator free days (12d vs. 10d)
- Laffey, John G., and Brian P. Kavanagh. "Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury." *N Engl J Med* 343.11 (2000): 812.


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 22, 2004 VOL. 351 NO. 4

Higher versus Lower Positive End-Expiratory Pressures in Patients with the Acute Respiratory Distress Syndrome

The National Heart, Lung, and Blood Institute ARDS Clinical Trials Network*

Mechanical Ventilation: Use of PEEP

- Randomly assigned 549 patients with ARDS to receive mechanical ventilation with either lower of higher PEEP levels, set according to different tables of predetermined combinations of PEEP and Fi02
- Conclusion: higher levels of PEEP/Fi02 does not improve outcomes
- Brower, R. G., et al. "Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome." *The New England journal of medicine* 351.4 (2004): 327-336.

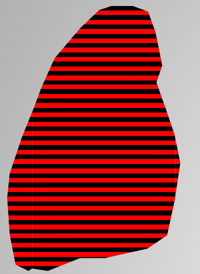
JAMA The Journal of the American Medical Association

Positive End-Expiratory Pressure Setting in Adults With Acute Lung Injury and Acute Respiratory Distress Syndrome
A Randomized Controlled Trial

Mechanical Ventilation: Use of PEEP

- Multicenter RCT of 767 adults with ARDS comparing a minimal distension strategy to increased recruitment strategy
- Conclusion: Increased recruitment strategy did not significantly reduce mortality, though improved lung function and reduced duration of mechanical ventilation and duration of organ failure
- Mercat, Alain, et al. "Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial." *Jama* 299.6 (2008): 646-655

Mechanical Ventilation: ARDSnet Protocol



INCLUSION CRITERIA: Acute onset of

1. $PaO_2/FiO_2 \leq 300$ (corrected for altitude)
2. Bilateral (patchy, diffuse, or homogeneous) infiltrates consistent with pulmonary edema
3. No clinical evidence of left atrial hypertension

PART I: VENTILATOR SETUP AND ADJUSTMENT

1. Calculate predicted body weight (PBW)
   Males = 50 + 2.3 [height (inches) - 60]
   Females = 45.5 + 2.3 [height (inches) -60]
2. Select any ventilator mode
3. Set ventilator settings to achieve initial V_T = 8 ml/kg PBW
4. Reduce V_T by 1 ml/kg at intervals $\leq$ 2 hours until V_T = 6ml/kg PBW.
5. Set initial rate to approximate baseline minute ventilation (not > 35 bpm).
6. Adjust V_T and RR to achieve pH and plateau pressure goals below.

ay

increase V_T in 1ml/kg increments to 7 or 8 ml/kg if Pplat remains $\leq$ 30 cm H_2O.

The NEW ENGLAND JOURNAL of MEDICINE

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*

Supportive therapy: Fluid Management

- Liberal vs. conservative fluid management
- Results support use of conservative fluid strategies in ARDS
- No significant difference in 60 day mortality
- Shortened duration of mechanical ventilation and ICU stay without compromising non-pulmonary organ failures
- Steingrub, M. D., and M. D. Tidswell. "Comparison of two fluid-management strategies in acute lung injury." (2006).

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Neuromuscular Blockers in Early Acute Respiratory Distress Syndrome

Laurent Papazian, M.D., Ph.D., Jean-Marie Forel, M.D., Arnaud Gacouin, M.D., Christine Penot-Ragon, Pharm.D., Gilles Perrin, M.D., Anderson Loundou, Ph.D., Samir Jaber, M.D., Ph.D., Jean-Michel Arnal, M.D., Didier Perez, M.D., Jean-Marie Seghboyan, M.D., Jean-Michel Constantin, M.D., Ph.D., Pierre Courant, M.D., Jean-Yves Lefrant, M.D., Ph.D., Claude Guérin, M.D., Ph.D., Gwenaël Prat, M.D., Sophie Morange, M.D., and Antoine Roch, M.D., Ph.D., for the ACURASYS Study Investigators

N Engl J Med 2010; 363:1107-1116 | September 16, 2010 | DOI: 10.1056/NEJMoa1005372

Supportive therapy: Neuromuscular blockade

- Multicenter trial with 340 patients
- Received 48 hours of Cisatracurium or placebo
- Conclusion: early administration of NBA improved 90 day survival and increased ventilator free days without increase in muscle weakness
- Papazian, Laurent, et al. "Neuromuscular blockers in early acute respiratory distress syndrome." *N Engl J Med* 363.12 (2010): 1107-1116.

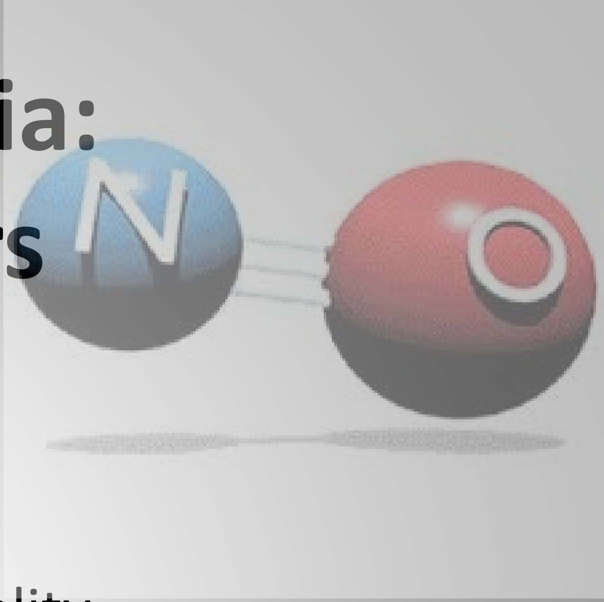
Supportive Therapy: Other

- Treat underlying infection
- DVT/stress ulcer prophylaxis
- HOB 30’
- Hand washing
- Full barriers with chlorhexadine
- Sedation/analgesia
- Nutrition
- Pressure ulcer prevention

Refractory Hypoxemia

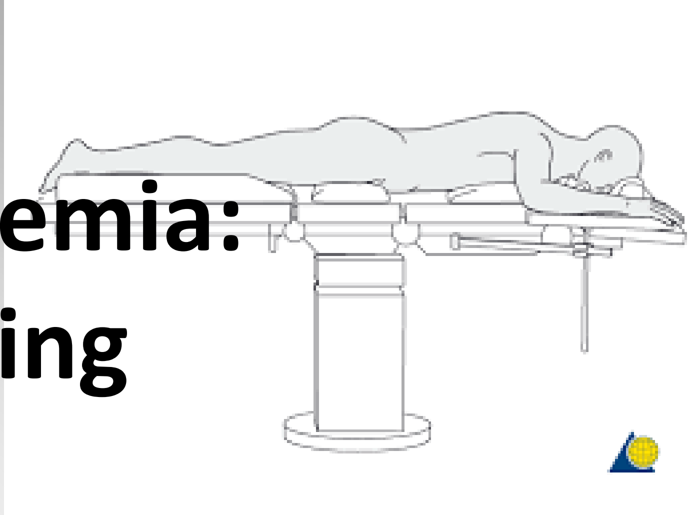
- Inhaled vasodilators
- Prone Positioning
- High frequency oscillatory ventilation
- Extracorporeal membrane oxygenation

Refractory Hypoxemia: Inhaled Vasodilators



- Nitric Oxide
  - Not a routine therapy
  - Improves oxygenation
  - Not shown to reduce morbidity or mortality
  - Used for intractable, life-threatening hypoxemia
- Prostacyclin
  - Comparable effects to iNO
  - Associated with improved in oxygenation and decreased in pulmonary artery pressure
  - Not shown to reduced morbidity or mortality
  - Does not require sophisticated equipment for administration

Refractory Hypoxemia: Prone Positioning



- Optimizes ventilation and perfusion
- Promotes alveolar recruitment
- First report dating back to 1976 (Piehl MA, Brown RS, Crit Care Med, 1976)
- First RCT evaluation prone positioning (Prone-Supine 1 Study), (Gattinoni et al., N Engl J Med, 2001): prone positioning reduced the 10-day mortality of patients with the highest disease severity (SAPS II>50)
  - Later reinforced

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 6, 2013 VOL. 368 NO. 23

Prone Positioning in Severe Acute Respiratory Distress Syndrome

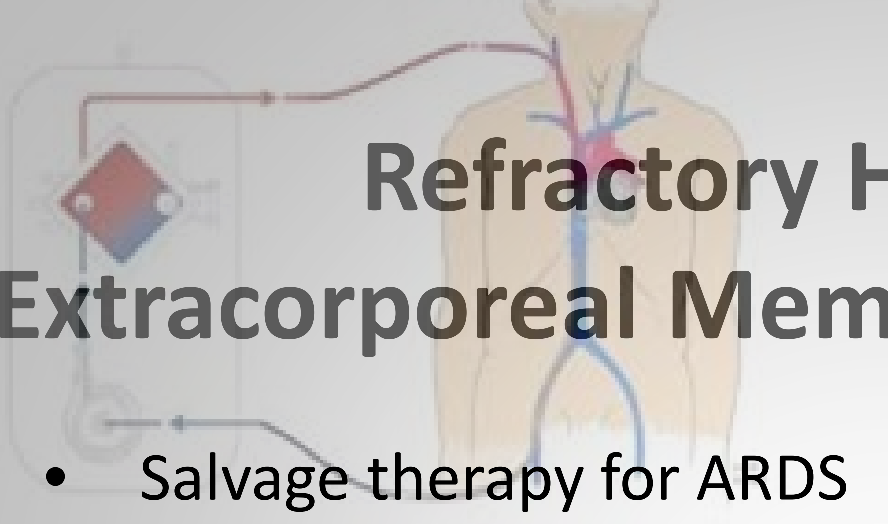
Claude Guérin, M.D., Ph.D., Jean Reignier, M.D., Ph.D., Jean-Christophe Richard, M.D., Ph.D., Pascal Beuret, M.D., Arnaud Gacouin, M.D., Thierry Boulain, M.D., Emmanuelle Mercier, M.D., Michel Badet, M.D., Alain Mercat, M.D., Ph.D., Olivier Baudin, M.D., Marc Clavel, M.D., Delphine Chatellier, M.D., Samir Jaber, M.D., Ph.D., Sylvène Rosselli, M.D., Jordi Mancebo, M.D., Ph.D., Michel Sirodot, M.D., Gilles Hilbert, M.D., Ph.D., Christian Bengler, M.D., Jack Richecoeur, M.D., Marc Gainnier, M.D., Ph.D., Frédérique Bayle, M.D., Gael Bourdin, M.D., Véronique Leray, M.D., Raphaele Girard, M.D., Loredana Baboi, Ph.D., and Louis Ayzac, M.D., for the PROSEVA Study Group*

PROSEVA

- 466 patients with severe ARDS (<36h after intubation)
  - P:F<150mmHg with FiO2>60% and PEEP>=5cm H2O
- Compared intermittent (16h daily) prone positioning to standard supine
- Incorporated LTVV and paralysis
- At 28 days prone group had a 51% relative and 17% absolute reduction in all-cause mortality when compared to the supine group
- Early application of prolonged prone positioning significantly decreased 28 day mortality in patients with severe ARDS
  - Guérin, Claude, et al. "Prone positioning in severe acute respiratory distress syndrome." *New England Journal of Medicine* 368.23 (2013): 2159-2168.

Prone positioning in practice

- Implement prone positioning early in the course (within 36 hours)
- Maintain prone positioning for 18-20 consecutive hours
- Low tidal volume ventilation
- Safety
- Absolute contraindications:
  - Spine instability
  - Unstable fractures
  - Anterior burns, open wounds
  - Pregnancy
  - Abdominal surgery



Refractory Hypoxemia: Extracorporeal Membrane Oxygenation

- Salvage therapy for ARDS
- Directly oxygenates and removes carbon dioxide from blood
- Blood withdrawn from central vein → ECMO circuit via pump → into oxygenator → returned to central vein
- Facilitates lung protective ventilation
- Role has not been definitely established
- Many uncertainties remain
- CESAR trial
  - 180 adults with ARDS randomly assigned to conventional management vs. specialized centers


The NEW ENGLAND JOURNAL of MEDICINE

The NEW ENGLAND JOURNAL of MEDICINE

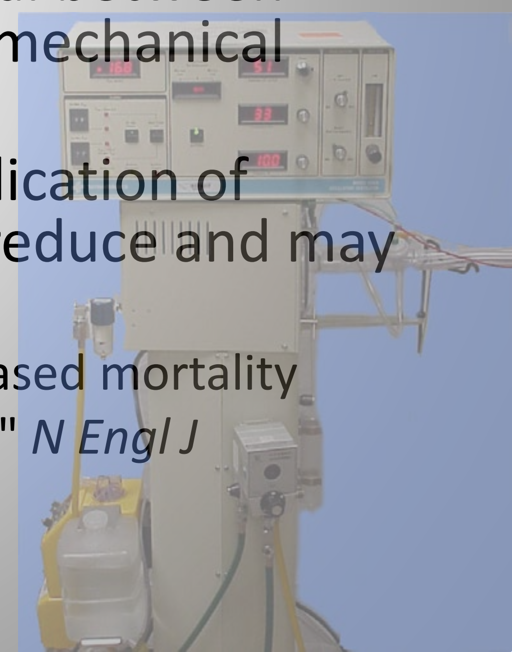
ORIGINAL ARTICLE

High-Frequency Oscillation for Acute Respiratory Distress Syndrome

Duncan Young, D.M., Sarah E. Lamb, D.Phil., Sanjoy Shah, M.D., Iain MacKenzie, M.D., William Tunnicliffe, M.Sc., Ranjit Lall, Ph.D., Kathy Rowan, D.Phil., and Brian H. Cuthbertson, M.D., for the OSCAR Study Group*

Refractory Hypoxemia: High Frequency Oscillatory Ventilation

- Delivers very small tidal volumes (~1-2mL/kg) at very high rates (3-15 breaths per second)
- Multicenter randomized trial with 795 patients enrolled
- Found no significant difference in 30 day survival between patients who received HFOV and conventional mechanical ventilation
- Larger multicenter trial revealed that early application of HFOV as compared with LTVV strategy did not reduce and may increase in-hospital mortality
  - Trial stopped early on basis of strong signal for increased mortality
  - Liaudet, Lucas. "High-frequency oscillation for ARDS." *N Engl J Med* 368.23 (2013): 2231.



Prognosis

- Mortality of ARDS ~26-58%
- In-hospital mortality improved over time
- Underlying cause of ARDS is the usual cause of death among patients who die early
- Sepsis due to nosocomial pulmonary infection is the most common cause of death among patients who die later in course
- Mortality increases with disease severity
- Risk of long term cognitive, psychological, and physical impairments

Assessment Question 1

Which of the following patients has severe ARDS?

a. A 65 year old woman admitted with 1 day of productive cough and fevers, tolerating 50% hi flow nasal cannula, with bilateral infiltrates on chest x-ray and a PaO2 of 160
b. A 25 year old woman admitted with 2 days of shortness of breath, complaining of “blue finger tips”, now intubated for severe hypoxemia with clear chest imaging and a p:f ratio of 68
c. A 36 year old man admitted with 4 days of productive cough and shortness of breath, now receiving mechanical ventilation with a large left sided infiltrate, a small right sided infiltrate and a p:f ratio of 80
d. A 68 year old man with known interstitial lung disease admitted with increased shortness of breath over the past 4 months, now receiving mechanical ventilation with a p:f ratio of 160

Assessment Question 2

Which intervention or therapy is appropriate for a patient with ARDS on invasive mechanical ventilation with a p:f of 250?

a. Prone positioning
b. Nitric oxide
c. Extracorporeal membrane oxygenation
d. Low tidal volume ventilation
e. B and D

Assessment Question 3

Which of the following supportive therapies have demonstrated a mortality benefit in the literature for patient with ARDS?

a. Paralysis
b. Prone positioning
c. Inhaled pulmonary vasodilators
d. A and B only
e. All of the above

Assessment Question 4

Which of the following statements is false?

a. Prostacyclin is associated with improved oxygenation and decreased pulmonary artery pressure
b. The optimal use of PEEP remains unclear
c. Conservative fluid management has demonstrated a reduction in days of mechanical ventilation and ICU stay
d. ARDS is a diagnosis and must be treated with low tidal volume ventilation in order for ARDS to resolve

QUESTIONS?