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

<table>
<thead>
<tr>
<th>Timing</th>
<th>Acute</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest Imaging</td>
<td>Bilateral opacities on chest x-ray</td>
</tr>
<tr>
<td>Origin of Edema</td>
<td>Absence of left atrial hypertension</td>
</tr>
<tr>
<td>Oxygenation</td>
<td>ARDS ( \rightarrow PaO_2/FiO_2 ) ratio less than 200</td>
</tr>
<tr>
<td></td>
<td>Acute Lung Injury ( \rightarrow PaO_2/FiO_2 ) ratio less than 300</td>
</tr>
</tbody>
</table>

### Berlin 2012 Definition

<table>
<thead>
<tr>
<th>Timing</th>
<th>Onset- Clarified “ within 1 week of known clinical insult or new symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest Imaging</td>
<td>Bilateral opacities not fully explained by lobar consolidation, collapse or nodules</td>
</tr>
<tr>
<td>Origin of Edema</td>
<td>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</td>
</tr>
<tr>
<td>Oxygenation</td>
<td>Mild ( 200&lt;PaO_2/FiO_2 \leq 300 ) CPAP or PEEP( \Rightarrow ) 5cms ( H_2O )</td>
</tr>
<tr>
<td></td>
<td>Moderate ( 100&lt;PaO_2/FiO_2 \leq 200 ) PEEP( \Rightarrow ) 5cms ( H_2O )</td>
</tr>
<tr>
<td></td>
<td>Severe ( PaO_2/FiO_2 \leq 100 ) PEEP( \Rightarrow ) 5cms ( H_2O )</td>
</tr>
</tbody>
</table>
**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!


---

**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
- FiO₂ use


**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
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

• 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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted OR (95% CI), P</th>
<th>Adjusted OR (95% CI), P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, per SD (16 y)</td>
<td>1.14 (1.02-1.28), .024</td>
<td>1.18 (1.02-1.38), .028</td>
</tr>
<tr>
<td>Sex, female</td>
<td>2.03 (1.61-2.58), .0001</td>
<td>NS</td>
</tr>
<tr>
<td>Race, white vs nonwhite</td>
<td>1.26 (0.99-1.60), .059</td>
<td>1.40 (1.05-1.88), .023</td>
</tr>
<tr>
<td>BMI per SD (7.3 kg/m²)</td>
<td>1.12 (0.99-1.26), .076</td>
<td>NS</td>
</tr>
<tr>
<td>Height, per SD (10 cm)</td>
<td>0.56 (0.50-0.64), .0001</td>
<td>0.55 (0.48-0.63), .0001</td>
</tr>
<tr>
<td>Weight, per SD (22 kg)</td>
<td>0.86 (0.77-0.97), .01</td>
<td>NS</td>
</tr>
<tr>
<td>SAPS II, per SD (14)</td>
<td>0.86 (0.77-0.97), .01</td>
<td>0.78 (0.67-0.92), .003</td>
</tr>
<tr>
<td>Direct lung injury</td>
<td>0.76 (0.59-0.98), .035</td>
<td>NS</td>
</tr>
<tr>
<td>Dialysis</td>
<td>3.80 (0.87-16.5), .075</td>
<td>NS</td>
</tr>
<tr>
<td>AIDS</td>
<td>0.64 (0.42-0.97), .036</td>
<td>NS</td>
</tr>
<tr>
<td>Radiographic lung injury score per SD (0.57)</td>
<td>0.64 (0.74-0.95), .005</td>
<td>0.83 (0.70-0.95), .009</td>
</tr>
<tr>
<td>Non-volume-control ventilator mode</td>
<td>3.18 (2.03-3.97), .0001</td>
<td>3.07 (1.78, 5.27), .0001</td>
</tr>
<tr>
<td>Serum bicarbonate per SD (5.5 mmol/L)</td>
<td>0.92 (0.82-1.03), .14</td>
<td>0.83 (0.71-0.97), .017</td>
</tr>
<tr>
<td>Duration of ICU stay before study enrollment per SD (2 d)</td>
<td>0.90 (0.80-1.01), .078</td>
<td>0.84 (0.73-0.98), .02</td>
</tr>
</tbody>
</table>

 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.
**Prevent over distension and under recruitment**

Video provided courtesy of Dr Christopher J. Farmer.

### High or Low PEEP?

<table>
<thead>
<tr>
<th>Control group</th>
<th>Exp group</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALVEOLI¹</td>
<td>6ml/kg and low PEEP</td>
<td>6ml/kg and high PEEP 80 pts recruitment maneuver</td>
</tr>
<tr>
<td>LOV²</td>
<td>6ml/kg and low PEEP</td>
<td>6 ml/kg and high PEEP Recruit if vent disconnect</td>
</tr>
<tr>
<td>EXPRESS³</td>
<td>6ml/kg, mod PEEP</td>
<td>6 ml/kg and PEEP to target plateau (28-30)</td>
</tr>
</tbody>
</table>

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

No difference in mortality
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)

Transpulmonary Pressure

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

How to set Optimal PEEP

- Recruitment potential - most important
- PEEP of zero (ZEEP) harmful in ARDS
- Usually 8-15 cm appropriate (up to 18 cm in studies), PEEP> 24 cm 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 25-30 cms
- 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 4 cms
  - May have to reduce PEEP by 2 cm decrements

Setting the Ventilator in ARDS for Lung Protective Ventilation

- Prefer Volume Control Mode
- $V_T = 6 \text{ ml/kg IBW}$
  - 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-$\text{FiO}_2$ tables, Driving Pressure
Setting the Ventilator in ARDS for Lung Protective Ventilation

- **Measure Plateau Pressure**, aim to limit less than 30 cm H$_2$O

- **Pay attention to patient size and chest wall**

- **Prevent patient ventilator dysynchrony**
  - NMB, heavy sedation

- **Adjust FiO$_2$ to target:**
  - PaO$_2$ 55-80 mmHg
  - SpO$_2$ 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 (SvO$_2$) and arterial oxygen saturation (SaO$_2$) in patients with an intrapulmonary shunt of 50%
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 PaCO2:44 PaO2=110
• MV mode: A/C
• RR: 18 per min
• Tidal Volume: 600cc (9 ml/kg)
• PEEP 6; FiO2 50%
What would you do next?

• 35 yo F, Day 2- post partum with acute onset dyspnea
• Ventilator settings:
  • FiO₂ 100%,
  • Peep 18 cms
  • TV: 320 (5cc/kg IBW)
  • RR 28,
  • Plateau pressure 28
• PaO₂/FiO₂ ratio : 57
• ABG: pH=7.20 PaCO₂ = 63 PaO₂= 57, bicarb: 21
• Transthoracic Echo: Acute RV failure, LV preserved
• Increasing vasopressor requirements

What next!

So you did all this, but the patient does not respond.
Life Saving Therapy In ARDS

Matthew Exline, MD
Associate Professor - Clinical
Department of Internal Medicine
Division of Pulmonary, Allergy, Critical Care and Sleep Medicine
The Ohio State University Wexner Medical Center

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
- $S_d =$ average osmotic coefficient
Diuresis
A Dry Lung is a Happy Lung

Increased in ARDS due to leaky capillaries

\[ Q_f = K_f c \left[ (P_{mv} - P_i) - (s_d)(T_{Tmv} - T_{Ti}) \right] \]

Increased in ARDS due to volume overload
Diuresis should help here

- 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

- **Arginine** → **NO**
- **NO Synthase**
- **Endothelial Cell**
- **Smooth Muscle Cell**
- **Smooth Muscle Relaxation**
- **cGMP**
- **Guanylyl Cyclase**
Mechanism Inhaled NO

A. Inspired Air

Healthy Alveoli

Diseased Alveoli

B. Healthy Alveoli

Diseased Alveoli

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 SaO₂

• 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
- Extracorporeal 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

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

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.

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

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. PaO₂ of 74mmHg on 50% FiO₂
- 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?

• 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

<table>
<thead>
<tr>
<th>What Buys Us Time</th>
<th>What Saves Lives!</th>
</tr>
</thead>
<tbody>
<tr>
<td>• PEEP</td>
<td>• Low Tidal Volume</td>
</tr>
<tr>
<td>• Diuresis</td>
<td>• Minimize Sedation</td>
</tr>
<tr>
<td>• Inhaled vasodilators</td>
<td>• Paralytics</td>
</tr>
<tr>
<td></td>
<td>• Prone Ventilation</td>
</tr>
<tr>
<td></td>
<td>• ECMO</td>
</tr>
<tr>
<td></td>
<td>• APRV (maybe)</td>
</tr>
</tbody>
</table>