Acute Respiratory Distress Syndrome (ARDS)

Sonal Pannu, MD
Clinical Assistant Professor
Department of Internal Medicine
Division of Pulmonary, Allergy, Critical Care and Sleep Medicine
The Ohio State University Wexner Medical Center

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><strong>Timing</strong></th>
<th>Acute</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chest Imaging</strong></td>
<td>Bilateral opacities on chest x-ray</td>
</tr>
<tr>
<td><strong>Origin of Edema</strong></td>
<td>Absence of left atrial hypertension</td>
</tr>
</tbody>
</table>
| **Oxygenation** | ARDS  
\(\text{PaO}_2/\text{FiO}_2\) ratio less than 200  
Acute Lung Injury  
\(\text{PaO}_2/\text{FiO}_2\) ratio less than 300 |

### Berlin 2012 Definition

<table>
<thead>
<tr>
<th><strong>Timing</strong></th>
<th>Onset- Clarified “ within 1 week of known clinical insult or new symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chest Imaging (CXR or CT scan)</strong></td>
<td>Bilateral opacities not fully explained by lobar consolidation, collapse or nodules</td>
</tr>
<tr>
<td><strong>Origin of Edema</strong></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>
</tbody>
</table>
| **Oxygenation**          | **Mild**  
200\(<\text{PaO}_2/\text{FiO}_2\) \leq 300  
CPAP or PEEP=> 5cms \(\text{H}_2\text{O}\)  

**Moderate**  
100\(<\text{PaO}_2/\text{FiO}_2\) \leq 200  
PEEP=> 5cms \(\text{H}_2\text{O}\)  

**Severe**  
\text{PaO}_2/\text{FiO}_2 \leq 100  
PEEP=> 5cms \(\text{H}_2\text{O}\) |
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**
- Pulmonary endothelial and alveolar epithelial injury → permeability edema
- Surfactant dysfunction
- Acute hypoxemia, increased dead space
- Venous admixture (V/Q mismatch)
- Low compliance
- Pulmonary Hypertension
- Poor weaning and possibly tracheostomy
- Poor long term pulmonary function

**Chronic Proliferative Phase**
- Maladaptive repair with mesenchymal cells and proliferative fibroblasts

**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

• FiO₂: 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

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>
<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 (1.05-1.86), .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>0.84 (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.

PEEP=“STABILIZE ALVEOLI”
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 6ml/kg and low PEEP</td>
<td>6ml/kg and high PEEP 80 pts recruitment maneuver</td>
<td>No difference in mortality</td>
</tr>
<tr>
<td>LOV² 6ml/kg and low PEEP</td>
<td>6 ml/kg and high PEEP Recruit if vent disconnect</td>
<td></td>
</tr>
<tr>
<td>EXPRESS³ 6ml/kg, mod PEEP</td>
<td>6 ml/kg and PEEP to target plateau (28-30)</td>
<td></td>
</tr>
</tbody>
</table>

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)

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 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 25-30 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 4cms
  - May have to reduce PEEP by 2 cm decrements

Setting the Ventilator in ARDS for Lung Protective Ventilation

- Prefer Volume Control Mode

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

- Measure Plateau Pressure, aim to limit less than 30 cm H₂O
- Pay attention to patient size and chest wall
- Prevent patient ventilator dysynchrony
  - NMB, heavy sedation
- Adjust FiO₂ 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%

What change would you make on the ventilator next?

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

What change would you make on the ventilator next?

<table>
<thead>
<tr>
<th>65yo intubated for airway protection with drug overdose</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABG pH: 7.38</td>
</tr>
<tr>
<td>PaCO2: 44 PaO2=110</td>
</tr>
<tr>
<td>MV mode: A/C</td>
</tr>
<tr>
<td>RR: 18 per min</td>
</tr>
<tr>
<td>Tidal Volume: 600cc (9 ml/kg)</td>
</tr>
<tr>
<td>PEEP 6; FiO2 50%</td>
</tr>
</tbody>
</table>
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

Source: MFMER

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

- \( Q_f = K_{fc} [(P_{mv} - P_i) - (s_a)(TT_{mv} - TT_i)] \)

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 Synthase
- Endothelial Cell
- Smooth Muscle Cell
- Guanylyl Cyclase
- cGMP

Smooth Muscle Relaxation

NO → NO Synthase

- Endothelial Cell
- Smooth Muscle Cell

- Guanylyl Cyclase
- cGMP

- Arginine → NO Synthase

- Endothelial Cell
- Smooth Muscle Cell

- Guanylyl Cyclase
- cGMP
Mechanism Inhaled NO

A. O₂ O₂ O₂ O₂ Healthy Alveoli Diseased Alveoli

Inspired Air

B. O₂ NO O₂

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….

**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**

- 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 breathe 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?

- 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</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>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>EXTRA EXTRA!</td>
<td></td>
</tr>
<tr>
<td>ARDS CURED!!</td>
<td></td>
</tr>
</tbody>
</table>