Acute Lung Injury and ARDS
The 1994 North American-European Consensus Conference (NAECC) criteria:

- **Onset** - Acute and persistent
- **Radiographic criteria** - Bilateral pulmonary infiltrates consistent with the presence of edema
- **Oxygenation criteria** - Impaired oxygenation regardless of the PEEP concentration, with a Pao$_2$/FiO$_2$ ratio $\leq$ 300 torr (40 kPa) for ALI and $\leq$ 200 torr (27 kPa) for ARDS
- **Exclusion criteria** - Clinical evidence of left atrial hypertension or a pulmonary-artery catheter occlusion pressure of $\geq$ 18 mm Hg.

*Bernard GR et al., Am J Respir Crit Care Med 1994*
The 1994 NAECC Definition Limitations

- Descriptive definition - Permits inclusion of a multiplicity of clinical entities ranging from autoimmune disorders to direct and indirect pulmonary injury
- Does not address the cause of lung injury
- Does not provide guidelines on how to define acute
- The radiological criteria are not sufficiently specific
- Does not account for the level of PEEP used, which affects the Pao$_2$/Fio$_2$ ratio
- Does not specify the presence of nonpulmonary organ system dysfunction at the time of diagnosis
- Does not include the different specific mechanistic pathways involved in producing lung injury

Atabai K and Matthay MA, Thorax 2000
Abraham E et al., Crit Care Med 2000
The 1998 NAECC Updated Recommendations

1. The collection of epidemiologic data should be based on the 1994 NAECC definitions.

2. The severity of ALI/ARDS should be assessed by the Lung Injury Score (LIS) or by the APACHE III or SAPS II scoring systems.

3. The factors that affect prognosis should be taken into account. The most important of these are incorporated into the GOCA stratification system.

4. It will be also useful to record:
   - Information relating to etiology (at a minimum, direct or indirect cause)
   - Mortality, including cause of death, and whether death was associated with withdrawal of care
   - Presence of failure of other organs and other time-dependent covariates
   - Follow-up information, including recovery of lung function and quality of life

Artigas A et al., Am J Respir Crit Care Med 1998
# Stratification System of Acute Lung Injury

**GOCA**

<table>
<thead>
<tr>
<th>Letter</th>
<th>Meaning</th>
<th>Scale</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>G</strong></td>
<td>Gas exchange</td>
<td>0</td>
<td>Pao$_2$/Fio$_2$ ≥ 301</td>
</tr>
<tr>
<td></td>
<td>Gas exchange (to be combined with the numeric descriptor)</td>
<td>1</td>
<td>Pao$_2$/Fio$_2$ 200 - 300</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>Pao$_2$/Fio$_2$ 101 - 200</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>Pao$_2$/Fio$_2$ ≤ 100</td>
</tr>
<tr>
<td></td>
<td>A</td>
<td></td>
<td>Spontaneous breathing, no PEEP</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td></td>
<td>Assisted breathing, PEEP 0-5 cmH$_2$O</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td></td>
<td>Assisted breathing, PEEP 6-10 cmH$_2$O</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td></td>
<td>Assisted breathing, PEEP ≥ 10 cmH$_2$O</td>
</tr>
<tr>
<td><strong>O</strong></td>
<td>Organ failure</td>
<td>A</td>
<td>Lung only</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B</td>
<td>Lung + 1 organ</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C</td>
<td>Lung + 2 organs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>D</td>
<td>Lung + ≥ 3 organs</td>
</tr>
<tr>
<td><strong>C</strong></td>
<td>Cause</td>
<td>1</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>Direct lung injury</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>Indirect lung injury</td>
</tr>
<tr>
<td><strong>A</strong></td>
<td>Associated diseases</td>
<td>0</td>
<td>No coexisting disease that will cause death within 5 yr</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>Coexisting disease that will cause death within 5 yr but not within 6 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>Coexisting disease that will cause death within 6 mo</td>
</tr>
</tbody>
</table>

NIH, 1972 - Incidence of ARDS in the United States: 75 cases per $10^5$ person.years population (approximately 150,000 cases per year)

International multi-center ALI/ARDS cohort studies, 1989 - 2002
- Incidence estimates of ALI/ARDS = 1.3 to 22 cases per $10^5$ person.years

ARDS Network Study (NAECC definitions), 2003 - Incidence of ALI/ARDS in the United States: 32 cases per $10^5$ person.years (range 16 - 64)

Goss CH et al., ARDS Network, Crit Care Med 2003
Clinical Disorders Associated with the Development of ALI/ARDS

Direct insult

Common
- Aspiration pneumonia
- Pneumonia

Less common
- Inhalation injury
- Pulmonary contusions
- Fat emboli
- Near drowning
- Reperfusion injury

Indirect insult

Common
- Sepsis
- Severe trauma
- Shock

Less common
- Acute pancreatitis
- Cardiopulmonary bypass
- Transfusion-related TRALI
- Disseminated intravascular coagulation
- Burns
- Head injury
- Drug overdose

Clinical Risk Factors Predictive of a Poor Outcome

Independent predictors repeatedly associated with higher mortality rates
- Severity of the illness (SAPS II and APACHE)
- Non-pulmonary organ dysfunction
- Comorbid diseases
- Sepsis
- Liver dysfunction/cirrhosis
- Advanced age

Other independent predictors
- Late ARDS (≥ 48 hours after MV initiation) or length of MV prior to ARDS
- Organ transplantation
- HIV infection
- Immunosuppression
- Active malignancy
- Oxygenation index (mean airway pressure x Fio2 x 100/Pao2)
- Mechanisms of lung injury
- Barotrauma
- Right ventricular dysfunction
- Fio2 (High Fio2)
- Pao2/Fio2<100 mmHg/Pao2/Fio2 on day 3
- Dead-space fraction
- Lower levels of PEEP or no PEEP
- Late respiratory acidosis
- McCabe score
- Chronic alcoholism

## Plasma Biologic Markers Predictive of a Poor Outcome

<table>
<thead>
<tr>
<th>Category</th>
<th>Biomarker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute inflammation</td>
<td>Interleukin(IL)-6, IL-8</td>
</tr>
<tr>
<td>Endothelial injury</td>
<td>von Willebrand factor antigen</td>
</tr>
<tr>
<td>Epithelial type II cell molecules</td>
<td>Surfactant protein-D</td>
</tr>
<tr>
<td>Adhesion molecule</td>
<td>Intercellular adhesion molecule-1 (ICAM-1)</td>
</tr>
<tr>
<td>Neutrophil-endothelial interaction</td>
<td>Soluble tumor necrosis factor receptors I and II (sTNFRI/II)</td>
</tr>
<tr>
<td>Procoagulant activity</td>
<td>Protein C</td>
</tr>
<tr>
<td>Fibrinolytic activity</td>
<td>Plasminogen activator inhibitor-1</td>
</tr>
</tbody>
</table>

Ware LB. Crit Care Med. 2005.
Mortality from ARDS

- ARDS mortality rates - 31% to 74%
- The variability in the rates quoted is related to differences in the populations studied and in the precise definitions used.
- The main causes of death are nonrespiratory causes (i.e., die with, rather than of, ARDS).
- Respiratory failure has been reported as the cause of death in 9% to 16% of patients with ARDS.
- Early deaths (within 72 hours) are caused by the underlying illness or injury, whereas late deaths are caused by sepsis or multiorgan dysfunction.
- There is a controversy about the role of hypoxemia as a prognostic factor in adults. Nevertheless, in some studies, both Pao$_2$/Fio$_2$ ratio and Fio$_2$ were variables independently associated to mortality.

Ware LB. Crit Care Med. 2005.
Persistent functional limitation

- **Extrapulmonary diseases (primarily):** Muscle wasting and weakness (corticosteroid-induced and critical-illness-associated myopathy)
- Entrapment neuropathy
- Heterotopic ossification
- **Intrinsic pulmonary morbidity (5%):** Bronchiolitis obliterans organizing pneumonia
- Bronchiolitis obliterans

Ventilatory-based Strategies in the Management of ARDS/ALI
Currently, the only therapy that has been proven to be effective at reducing mortality in ALI/ARDS in a large, randomized, multi-center, controlled trial is a protective ventilatory strategy.

Tidal volume and plateau pressure
Ventilator-induced Lung Injury Conceptual Framework

Lung injury from:
- Overdistension/shear -> physical injury
- Mechanotransduction -> “biotrauma”
- Repetitive opening/closing
- Shear at open/collapsed lung interface

Systemic inflammation and death from:
- Systemic release of cytokines, endotoxin, bacteria, proteases

“volutrauma”
“atelectrauma”
Ventilator-induced Lung Injury

Three different pathologic entities:

- High-permeability type pulmonary edema
- Mechanical over-inflation/distortion of lung structures
- Lung inflammation “Biotrauma”

Ventilator-induced Lung Injury

High-permeability type pulmonary edema

Mechanisms altering the alveolar-capillary barrier permeability during MV involve:
- Increased transmural vascular pressure
- Surfactant inactivation
- Mechanical distortion and disruption of endothelial cells
- Regional activation of inflammatory cells

Ventilator-induced Lung Injury

Mechanical overinflation/distortion of lung structures

- Emphysema-like lesions, lung cysts, and bronchiectasis
- These lesions predominate in nondependent and caudal lung regions
- The degree of overinflation is dependent on:
  - Tidal volume
  - Peak airway pressure
  - Duration of mechanical ventilation
  - Time exposed to an Fio$_2$ > 0.6

Ventilator-induced Lung Injury

Lung inflammation “biotrauma”

- Lung overinflation or overstretching produces regional and systemic inflammatory response that may generate or amplify multiple-system organ failure.
- Factors converting the shear stress applied to an injured lung into regional and systemic inflammation are still incompletely elucidated but could include:
  - Repetitive opening and collapse of atelectatic lung units
  - Surfactant alterations
  - Loss of alveolo-capillary barrier function
  - Bacterial translocation
  - Overinflation of health lung regions

Ventilator-induced Lung Injury

Two primary mechanistic factors:

- Overdistension of the alveoli by high transpulmonary pressures: volutrauma
- Shear-stress forces produced by repetitive alveolar recruitment and derecruitment (collapse)

Animal data so compelling that in early 1990s the SCCM and ACCP recommended reduction in tidal volume and limiting end-expiratory plateau pressure to < 35 cm H$_2$O
Tidal Volume Strategies in ARDS

**Traditional Approach**
- High priority to traditional goals of acid-base balance and patient comfort
- Lower priority to lung protection

**Low Stretch Approach**
- High priority to lung protection
- Lower priority to traditional goals of acid-base balance and comfort
ARDS Net Study 01: Hypothesis

In patients with ALI/ARDS, ventilation with reduced tidal volume will limit “volutrauma” and improve survival.

“Lung-protective strategies”

Patients with ALI/ARDS (NAECC definitions) of < 36 hours

Ventilator procedures
- Volume-assist-control mode
- RCT of 6 vs. 12 ml/kg of predicted body weight PBW Tidal Volume (PBW/Measured body weight = 0.83)
- Plateau pressure ≤ 30 vs. ≤ 50 cmH$_2$O
- Ventilator rate setting 6-35 (breaths/min) to achieve a pH goal of 7.3 to 7.45
- I/E ratio: 1.1 to 1.3
- Oxygenation goal: PaO$_2$ 55 - 80 mmHg/SpO$_2$ 88 - 95%
- Allowable combination of FiO$_2$ and PEEP:

<table>
<thead>
<tr>
<th>FiO$_2$</th>
<th>0.3</th>
<th>0.4</th>
<th>0.4</th>
<th>0.5</th>
<th>0.6</th>
<th>0.7</th>
<th>0.7</th>
<th>0.8</th>
<th>0.9</th>
<th>0.9</th>
<th>0.9</th>
<th>1.0</th>
<th>1.0</th>
<th>1.0</th>
<th>1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEEP</td>
<td>5</td>
<td>5</td>
<td>8</td>
<td>8</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>12</td>
<td>14</td>
<td>14</td>
<td>14</td>
<td>16</td>
<td>18</td>
<td>18</td>
<td>20</td>
</tr>
</tbody>
</table>

The trial was stopped early after the fourth interim analysis (n = 861 for efficacy; p = 0.005 for the difference in mortality between groups)
ARDS Network: Improved Survival with Low $V_T$

- **Lower tidal volumes**
  - Survival
  - Discharge

- **Traditional tidal values**
  - Survival
  - Discharge

Days after Randomization

### ARDS Network: Main Outcome Variables

<table>
<thead>
<tr>
<th></th>
<th>Low Vt</th>
<th>Traditional Vt</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death before discharge home and breathing without assistance (%)</td>
<td>31.0</td>
<td>39.8</td>
<td>0.007</td>
</tr>
<tr>
<td>Breathing without assistance by day 28 (%)</td>
<td>65.7</td>
<td>55.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>No. of ventilator-free days, days 1 to 28</td>
<td>12 ± 11</td>
<td>10 ± 11</td>
<td>0.007</td>
</tr>
<tr>
<td>Barotrauma, days 1 to 28 (%)</td>
<td>10</td>
<td>11</td>
<td>0.43</td>
</tr>
<tr>
<td>No. of days without failure of nonpulmonary organs or systems, days 1 to 28</td>
<td>15 ± 11</td>
<td>12 ± 11</td>
<td>0.006</td>
</tr>
</tbody>
</table>

In ALI and ARDS patients, 6 ml/kg PBW tidal volume ventilation strategy was associated with:

• PaO$_2$/FiO$_2$ lower in 6 ml/kg low V$_T$ group
• High RR prevented hypercapnia with minimal auto-PEEP (difference of median intrinsic PEEP between the groups was < 1 cm H$_2$O)
• No difference in their supportive care requirements (vasopressors-IV fluids-fluid balance-diuretics-sedation)
• ~10% mortality reduction
• Less organ failures
• Lower blood IL-6 and IL-8 levels

Ventilator-induced Lung Injury

Two primary mechanistic factors:

- **Overdistension of the alveoli by high transpulmonary pressures**
- **Shear-stress forces produced by repetitive alveolar recruitment and derecruitment (collapse) - Atelectrauma**

In animal models, the repetitive cycle of alveolar collapse and re-recruitment has been associated with worsening lung injury. The extent of this injury has been reduced in animals through the use of PEEP levels that prevent derecruitment at end-expiration.
Significant prognostic factors responsible of the ventilatory treatment effect:

- APACHE II score
- Mean PEEP during the first 36 hours (with a protective effect)
- Driving pressures (PPLAT - PEEP) during the first 36 hours

PEEP in ARDS
How much is enough?

- PEEP by avoiding repetitive opening and collapse of atelectatic lung units, could be protective against VILI.
- High PEEP should make the mechanical ventilation less dangerous than low PEEP.
- The recruitment is obtained essentially at end-inspiration, and the lung is kept open by using PEEP to avoid end-expiratory collapse.
- PEEP, by preserving inspiratory recruitment and reestablishing end-expiratory lung volume, has been shown to prevent surfactant loss in the airways and avoid surface film collapse.

PEEP in ARDS
How much is enough?

“Optimal PEEP”: Allowing for a given ARDS an optimization of arterial oxygenation without introducing a risk of oxygen toxicity and VILI, while having the least detrimental effect on hemodynamics, oxygen delivery, and airway pressures.

There has never been a consensus regarding the optimum level of PEEP for a given patient with ARDS.

The potential for recruitment may largely vary among the ALI/ARDS population.

PEEP may increase PaO₂ without any lung recruitment because of a decrease in and/or a different distribution of pulmonary perfusion.

In patients with ALI/ARDS (NAECC definitions) of < 36 hours who receive mechanical ventilation with a $V_T$ of 6 ml/kg of PBW, higher PEEP may improve clinical outcomes.
NIH-NHLBI ARDS Network

- Patients with ALI/ARDS (NAECC definitions) of < 36 hours

- Ventilator procedures
  - Volume-assist-control mode
  - Tidal-volume goal: 6 ml/kg of predicted body weight PBW
  - Plateau pressure ≤ 30 cm H₂O
  - Ventilator rate setting 6 - 35 (breaths/min) to achieve a pH goal of 7.3 if possible
  - I/E ratio: 1.1 to 1.3
  - Oxygenation goal: PaO₂ 55 - 80 mmHg/SpO₂ 88 - 95%
  - Allowable combination of FiO₂ and PEEP:

<table>
<thead>
<tr>
<th>Low PEEP</th>
<th>FiO₂</th>
<th>0.3</th>
<th>0.4</th>
<th>0.4</th>
<th>0.5</th>
<th>0.5</th>
<th>0.6</th>
<th>0.7</th>
<th>0.7</th>
<th>0.8</th>
<th>0.9</th>
<th>0.9</th>
<th>0.9</th>
<th>1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEEP</td>
<td>5</td>
<td>5</td>
<td>8</td>
<td>8</td>
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<td>10</td>
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<td>12</td>
<td>14</td>
<td>14</td>
<td>14</td>
<td>14</td>
<td>16</td>
<td>18-24</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>High PEEP</th>
<th>FiO₂</th>
<th>0.3</th>
<th>0.3</th>
<th>0.4</th>
<th>0.4</th>
<th>0.5</th>
<th>0.5</th>
<th>0.5-0.8</th>
<th>0.8</th>
<th>0.9</th>
<th>1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEEP</td>
<td>12</td>
<td>14</td>
<td>14</td>
<td>16</td>
<td>16</td>
<td>18</td>
<td>20</td>
<td>22</td>
<td>22</td>
<td>22-24</td>
<td></td>
</tr>
</tbody>
</table>

- The trial was stopped early after the second interim analysis (n = 549 on the basis of the specified futility stopping rule).
NIH-NHLBI ARDS Network
FiO₂-PEEP Step Comparison

![Graph showing FiO₂-PEEP Step Comparison](image-url)
NIH-NHLBI ARDS Network
Cause of Lung Injury

- Sepsis: 22%
- Trauma: 8%
- Aspiration: 15%
- Transfusion: 5%
- Pneumonia: 40%
- Other: 10%

NIH-NHLBI ARDS Network
Clinical Outcomes

Lower PEEP, overall survival
Higher PEEP, overall survival
Lower PEEP, discharge
Higher PEEP, discharge

## NIH-NHLBI ARDS Network
### Main Outcome Variables

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Lower-PEEP group</th>
<th>Higher-PEEP group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death before discharge home (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>24.9</td>
<td>27.5</td>
<td>0.48</td>
</tr>
<tr>
<td>Adjusted for difference in baseline covariance</td>
<td>27.5</td>
<td>25.1</td>
<td>0.47</td>
</tr>
<tr>
<td>Breathing without assistance by day 28 (%)</td>
<td>72.8</td>
<td>72.3</td>
<td>0.89</td>
</tr>
<tr>
<td>No. of ventilator-free days from day 1 to day 28</td>
<td>14.5 ± 10.5</td>
<td>13.8 ± 10.6</td>
<td>0.50</td>
</tr>
<tr>
<td>No. of days not spent in ICU from day 1 to day 28</td>
<td>12.2 ± 10.4</td>
<td>12.3 ± 10.3</td>
<td>0.83</td>
</tr>
<tr>
<td>Barotrauma (%)</td>
<td>10</td>
<td>11</td>
<td>0.51</td>
</tr>
<tr>
<td>No. of days without failure of circulatory, coagulation, hepatic, and renal organs from day 1 to day 28</td>
<td>16 ± 11</td>
<td>16 ± 11</td>
<td>0.82</td>
</tr>
</tbody>
</table>

In ALI and ARDS patients, higher PEEP strategy was associated with:
• \( \text{PaO}_2/\text{FiO}_2 \) higher the first seven days post randomization
• Plateau pressure higher the first three days post randomization
• \( V_T \) lower the first three days post randomization
• No difference in RR, \( \text{PaCO}_2 \), or pH
• No difference in mortality rate
• No difference in organ failures or barotrauma
• No difference in IL-6, ICAM-1, surfactant protein-D
Why is higher PEEP not better in this study?

- Beneficial effects of higher PEEP counteracted by adverse effects?
- Recruitment maneuvers are needed?
- “Lower PEEP” (or lower tidal volume) was sufficient to protect against injury from “atelectrauma” (ventilation at low end-expiratory volumes)?

Lung Recruitment

- First and foremost performed to provide an arterial oxygen saturation of 90% or greater at an $\text{Fio}_2$ of less than 60%
- Recruitment of nonaerated lung units (open-lung concept) but risk of regional lung overinflation is a highly controversial issue
The ARDS Lungs

- Increase in lung density from alveolar edema and inflammation that predominates in cephalic parts of the lungs

- Loss of aeration (lung collapse) that predominates in caudal and dependent lung regions in patients lying supine
  - External compression of caudal parts of the lungs by an enlarged heart (myocardial edema, hyperdynamic profile, and pulmonary hypertension-induced right ventricular dilatation)
  - High pressure exerted by the abdominal content
  - Accumulation of fluid in the pleural space
  - Own increased weight (gravitation forces-weight of the edematous lung)

- Consolidated alveoli - Alveolar flooding: Fluid-filled alveoli (edema fluid or inflammatory cells) that predominates in caudal and dependent lung regions in patients lying supine
The ARDS Lungs

External forces applied on the lower lobes at end inspiration and end expiration in a patient in the supine position and mechanically ventilated with positive end-expiratory pressure.

- Large blue arrows: Forces resulting from tidal ventilation
- Small blue arrows: Forces resulting from positive end-expiratory pressure (PEEP)
- Green arrows: Forces exerted by the abdominal content and the heart on the lung

# The ARDS Lungs

<table>
<thead>
<tr>
<th>ARDS</th>
<th>Focal</th>
<th>Patchy</th>
<th>Diffuse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest x-ray (zero PEEP)</td>
<td>Focal heterogeneous loss of aeration in caudal and dependent lung region</td>
<td>Bilateral and diffuse x-ray densities respecting lung apices</td>
<td>Bilateral and diffuse hyperdensities “White lungs”</td>
</tr>
<tr>
<td>Chest CT scan (zero PEEP)</td>
<td>Upper lobes normally aerated despite a regional excess of lung tissue – Lower lobes poorly or non aerated</td>
<td>Lower lobes massively nonaerated – The loss of aeration involves partially the upper lobes</td>
<td>Massive, diffuse and bilateral non- or poorly aerated lung regions – No normally aerated lung region</td>
</tr>
<tr>
<td>Response to PEEP</td>
<td>± PEEP &lt;10-12 cmH₂O</td>
<td></td>
<td>+++++ Lung recruitment curve Open lung concept</td>
</tr>
<tr>
<td>Risk of overinflation of the aerated lung regions</td>
<td>++++</td>
<td></td>
<td>±</td>
</tr>
<tr>
<td>Recruitment of non aerated lung unit</td>
<td>Low potential for recruitment</td>
<td></td>
<td>High potential for recruitment</td>
</tr>
</tbody>
</table>

## The ARDS Lungs

<table>
<thead>
<tr>
<th>Early phases of ARDS</th>
<th>Direct insult of the lung</th>
<th>“Indirect” insult of the lung</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Primary pulmonary ARDS</td>
<td>Secondary extrapulmonary ARDS</td>
</tr>
<tr>
<td>Pathologic changes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung tissue consolidation</td>
<td>Severe intra-alveolar damage</td>
<td>Microvascular congestion</td>
</tr>
<tr>
<td></td>
<td>(Edema, fibrin, collagen</td>
<td>Interstitial edema</td>
</tr>
<tr>
<td></td>
<td>neutrophil aggregates,</td>
<td>Alveolar collapse</td>
</tr>
<tr>
<td></td>
<td>red cells)</td>
<td>Less severe alveolar damage</td>
</tr>
<tr>
<td>End-expiratory lung volume EELV</td>
<td>↓↓↓</td>
<td>↓↓↓</td>
</tr>
<tr>
<td>Static elastance of the total respiratory system Est,rs</td>
<td>↑↑↑↑</td>
<td>↑↑↑↑</td>
</tr>
<tr>
<td>Static elastance of the chest wall Est,w / Static lung elastance Est,L</td>
<td>↑ / ↑↑↑</td>
<td>↑↑ / ↑</td>
</tr>
<tr>
<td>Intra-abdominal pressure</td>
<td>↑</td>
<td>↑↑↑</td>
</tr>
<tr>
<td>Response to PEEP</td>
<td>Est,rs ↑↑↑ [Est,L &gt;&gt; Est,w] Stretching phenomena</td>
<td>Est,rs ↓↓↓ [Est,L ≈ Est,w] Recruitment of previously closed alveolar spaces</td>
</tr>
<tr>
<td>Lung recruitment</td>
<td>±</td>
<td>++++</td>
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Respiratory Pressure/Volume (P/V) Curve

Healthy subject

In normal healthy volunteers, the P/V curve explores the mechanical properties of the respiratory system (lung + chest wall).

ARDS

RV, Residual volume; FRC, Functional residual capacity; TLC, Total lung capacity; UIP, Upper inflection point; LIP, Lower inflection point. The critical opening pressure above which most of the collapsed units open up and may be recruited - CLIN Compliance of the intermediate, linear segment of the P/V curve.

Measurement of the P/V curve in any given patient is not practical clinically.

A single inflation P/V curve probably does not provide useful information to determine safe ventilator settings in ALI.

The P/V curve for the whole lung is a composite of multiple regional P/V curves (considerable variation from the dependent to the nondependent lung; LIP from 50 to 30 cmH₂O respectively).
Recruitment Maneuvers (RM)s

- Proposed for improving arterial oxygenation and enhancing alveolar recruitment

- All consisting of short-lasting increases in intrathoracic pressures
  - Vital capacity maneuver (inflation of the lungs up to 40 cm H₂O, maintained for 15 - 26 seconds) (Rothen HU. BJA. 1999; BJA 1993.)
  - Intermittent sighs (Pelosi P. Am J Respir Crit Care Med. 2003.)
  - Extended sighs (Lim CM. Crit Care Med. 2001.)
  - Intermittent increase of PEEP (Foti G. Intensive Care Med. 2000.)
  - Increasing the ventilatory pressures to a plateau pressure of 50 cm H₂O for 1-2 minutes (Marini JJ. Crit Care Med. 2004. Maggiore SM. Am J Respir Crit Care Med. 2003.)

Lapinsky SE and Mehta S, Critical Care 2005
Recruitment Maneuvers (RMs)

Effective in improving arterial oxygenation only at low PEEP and small tidal volumes. When alveolar recruitment is optimized by increasing PEEP, recruitment maneuvers are either poorly effective or deleterious, inducing overinflation of the most compliant regions, hemodynamic instability, and an increase in pulmonary shunt resulting from the redistribution of pulmonary blood flow toward nonaerated lung regions.

The effect of recruitment may not be sustained unless adequate PEEP is applied to prevent derecruitment.

Many questions still need to be answered:

- Optimal time to perform RMs (First hours after endotracheal intubation, early phase of ARDS, after endotracheal suctioning)
- How often they should be used
- Their durations
- The recommended ventilatory mode (CPAP, sighs, pressure controlled ventilation, short duration high PEEP level)
- The long-lasting effects of RMs on ABGs are contradictory.
High-frequency Oscillatory Ventilation

Characterized by rapid oscillations of a reciprocating diaphragm, leading to high-respiratory cycle frequencies, usually between 3 and 9 Hz in adults, and very low $V_T$. Ventilation in HFOV is primarily achieved by oscillations of the air around the set mean airway pressure mPaw.

HFOV is conceptually very attractive, as it achieves many of the goal of lung-protective ventilation.

- Constant mPaws: Maintains an “open lung” and optimizes lung recruitment
- Lower $V_T$ than those achieved with controlled ventilation (CV), thus theoretically avoiding alveolar distension.
- Expiration is active during HFOV: Prevents gas trapping
- Higher mPaws (compared to CV): Leads to higher end-expiratory lung volumes and recruitment, then theoretically to improvements in oxygenation and, in turn, a reduction of $F_{iO_2}$.

Chan KPW and Stewart TE, Crit Care Med 2005
High-frequency Oscillatory Ventilation

Observational studies have demonstrated that HFOV may improve oxygenation when used as a rescue modality in adult patients with severe ARDS failing CV.

- Preliminary data suggest that there may be a survival advantage.

HFOV may be considered for patients with severe ARDS:

- \( F_{\text{O}_2} > 0.60 \) and/or \( \text{SpO}_2 < 88\% \) on CV with PEEP > 15 cm H\textsubscript{2}O, or
- Plateau pressures (Pplat) > 30 cmH\textsubscript{2}O, or
- Mean airway pressure \( \geq 24 \text{ cm H}_2\text{O} \), or
- Airway pressure release ventilation \( P_{\text{high}} \geq 35 \text{ cm H}_2\text{O} \)

- “Team approach” (attending physician, respiratory care team leader, respiratory care area manager, critical care nurse, ICU respiratory therapist)

HFOV for adults with ARDS is still in its infancy and requires further evaluations.

Higgins J et al., Crit Care Med 2005
**Non-ventilatory-based Strategies in the Management of ARDS/ALI**

- Fluid and hemodynamic management
- Inhaled nitric oxide
- Prone position ventilation
- Steroids
- Other drug therapy
**Fluid and Hemodynamic Management**

**Starling Equation**

\[ Q_f = K_f \left[ (P_c - P_{IF}) - s(p_c - p_{IF}) \right] \]

- \( K_f \): capillary filtration coefficient
- \( P_{IF} \): interstitial hydrostatic pressure
- \( p_c \): capillary colloid osmotic pressure
- \( P_c \): capillary hydrostatic pressure
- \( s \): oncotic reflection coefficient
- \( p_{IF} \): interstitial colloid oncotic pressure

**Pathophysiology:**

- Increases in capillary hydrostatic pressure
- Increased membrane permeability
- Diminished oncotic pressure gradient

**Clinical implications:**

- Reductions in pulmonary capillary hydrostatic pressure/pulmonary artery occlusion pressure – CVP
- Hemodynamic monitoring to avoid tissue hypoperfusion
- Fluid restriction/negative fluid balance
- Diuretics
- Combination therapy with colloids and furosemide?

Lewis CA and Martin GS, Curr Opin Crit Care 2004
Klein Y, J Trauma 2004
**Inhaled Nitric Oxide**

- **Physiology of inhaled nitric oxide therapy**
  - Selective pulmonary vasodilatation (decreases arterial and venous resistances)
  - Decreases pulmonary capillary pressure
  - Selective vasodilatation of ventilated lung areas
  - Bronchodilator action
  - Inhibition of neutrophil adhesion
  - Protects against tissue injury by neutrophil oxidants

Effects of Inhaled Nitric Oxide in Patients with Acute Respiratory Distress Syndrome: Results of a Randomized Phase II Trial

In patients with documented ARDS, iNO at 1.25, 5, 20, 40, or 80 ppm:

- Is associated with a significant improvement in oxygenation compared with placebo over the first four hours of treatment. An improvement in oxygenation index was observed over the first four days.
- Acutely increased the PaO₂ in 60% of the patients.
- The percentage of patients having an acute increase in PaO₂ and the magnitude of the change were similar in each of the inhaled NO dose groups.
- Appears to be well tolerated in doses between 1.25 to 40 ppm.
- Although these concentrations appear to be safe, it would be prudent to more closely monitor NO₂ concentrations, and methemoglobin.
- There are trends in decreasing the intensity of mechanical ventilation needed to maintain adequate oxygenation and improved patient benefit at 5 ppm inhaled NO.

Dellinger RP et al., Crit Care Med 1998
Low-dose Inhaled Nitric Oxide in Patients with Acute Lung Injury: A Randomized Controlled Trial

In patients with documented ARDS and severe acute lung injury (PaO$_2$/FiO$_2$ ≤ 250) but without sepsis or other organ system failure, iNO at 5 ppm:

- Induces short-term improvements in oxygenation with a 20% increase in PaO$_2$ that were maintained only during 24 - 48 hours.
- Does not improve clinical outcomes or mortality

These data do not support the routine use of inhaled nitric oxide in the treatment of acute lung injury or ARDS.

Inhaled nitric oxide may be considered (Grade C recommendation) as a salvage therapy in acute lung injury or ARDS patients who continue to have life threatening hypoxemia despite optimization of conventional mechanical ventilator support.

Prone Positioning

- Limits the expansion of cephalic and parasternal lung regions
- Relieves the cardia and abdominal compression exerted on the lower lobes
- Makes regional ventilation/perfusion ratios and chest elastance more uniform
- Facilitates drainage of secretions
- Potentiates the beneficial effect of recruitment maneuvers
Prone Positioning

**Absolute contraindications**
- Burns or open wounds on the face or ventral body surface
- Spinal instability
- Pelvic fractures
- Life-threatening circulatory shock
- Increased intracranial pressure

**Main complications**
- Facial and periorbital edema
- Pressure sores
- Accidental loss-displacement of the endotracheal tube, thoracic or abdominal drains, and central venous catheters
- Airway obstruction
- Hypotension
- Arrhythmias
- Vomiting
Prone Positioning

- Improves arterial oxygenation in more than 70% of patients in early stage of ARDS (a decrease in FiO₂ ≥ 20% is expected)
- No baseline features that differentiate between responders and non responders are known.
- After the patient back to the supine position, the oxygenation might return to the basal supine value, or remain elevated
- Does not increase survival at the end of the 10-day study period, at the time of discharge from the ICU, or at six months
- However in the most severely ill and hypoxemic patients with a Pao₂/Fio₂ ≤ 88 mmHg, a, SAPS II > 49, a high tidal volume > 12 ml/kg of PBW, or all three, it may reduce mortality and limit VILI.
- The optimum daily duration is not known. In clinical practice, the duration ranges between six and 12 hours/day.
- The optimum total duration and number of pronations depends on the effects on arterial oxygenation of supine repositioning

Effect of Prone Positioning on the Survival of Patients with Acute Respiratory Failure

Enrollment:
- Oxygenation criteria
  \[ \text{Pao}_2/\text{FiO}_2 \leq 200 \text{ with a PEEP } \geq 5 \text{ cm H}_2\text{O} \]
  \[ \text{Pao}_2/\text{FiO}_2 \leq 300 \text{ with a PEEP } \geq 10 \text{ cm H}_2\text{O} \]
- Radiographic criteria
  Bilateral pulmonary infiltrates
- Pulmonary-capillary wedge pressure \( \leq 18 \text{ mm Hg} \) or the absence of clinical evidence of left atrial hypertension.

Treatment protocol:
After randomization, prone group patients were continuously kept prone for at least six hours per day for a period of 10 days.

Effect of Prone Positioning on the Survival of Patients with Acute Respiratory Failure

Kaplan-Meier estimates of survival at six months

Effect of Prolonged Methylprednisolone in Unresolving ARDS

**Rationale:** Within seven days of the onset of ARDS, many patients exhibit a new phase of their disease marked by fibrotic lung disease or fibrosing alveolitis with alveolar collagen and fibronectin accumulation.

**Patient selection:** Severe ARDS/≥7 days of mechanical ventilation with an LIS ≥ 2.5/No evidence of untreated infection

**Treatment protocol:** Methylprednisolone
- Loading dose 2 mg/kg
- 2 mg/kg/24 hours from day 1 to day 14
- 1 mg/kg/24 hours from day 15 to day 21
- 0.5 mg/kg/24 hours from day 22 to day 28
- 0.25 mg/kg/24 hours on days 29 and 30
- 0.125 mg/kg/24 hours on day 31 and 32

In patients with unresolving ARDS, prolonged administration of methylprednisolone was associated with improvement in lung injury and MODS scores and reduced mortality.

Meduri GU et al., JAMA 1998
Corticosteroid Therapy in ARDS: Better late than never?

High-dose corticosteroids in early ARDS
- Do not lessen the incidence of ARDS among patients at high risk
- Do not reverse lung injury in patients with early ARDS/worse recovery
- Have no effect on mortality/even increase mortality rate
- Significantly increase the incidence of infectious complications

High-dose corticosteroids for unresolving ARDS of \( \geq 7 \) days duration who do not have uncontrolled infection
- There are several challenges associated with the interpretation of this trial. A large clinical trial is needed to clearly demonstrate a survival advantage that outweighs the potential risks.
- Patient selection: Lack of clinical improvement rather than use of only the LIS
- Aggressive search for and treatment of infectious complications is necessary.
- Several questions remain: Timing, dosage, and duration of late steroid therapy in ARDS/Appropriate time window for corticosteroid administration, between early acute injury and established postagressive fibrosis.

Kopp R et al., Intensive Care Med 2002
Brun-Buisson C and Brochard L, JAMA 1998
Other Drug Therapy

- Prostaglandin E1 (PGE1) (pulmonary vasodilatation and anti-inflammatory effects on neutrophils/macrophages)
- Aerosolized prostacyclin (PGI2) (selective pulmonary vasodilatation of ventilated lung areas)
- Almitrine (selective pulmonary vasoconstrictor of nonventilated lung areas)
- Surfactant (prevents alveolar collapse and protects against intrapulmonary injury and infection)
- Antioxidants (protect the lung from free oxygen radical production)
- Partial liquid ventilation (recruitment of collapsed areas and anti-inflammatory effect)
- Anti-inflammatory drugs (Ibuprofen - ketoconazole)
- No recommendation can be made for their use - Rescue modality in the patient with refractory hypoxia?
Combination of different therapeutic approaches?

- Combination of iNO and prone position (Papazian L, et al. Crit Care Med. 1998.)
- Combination of iNO and almitrine (Gallart L, et al. Am J Respir Crit Care Med. 1998.)
- Combination of iNO and iv prostacycline (Kuhlen R, et al. Intensive Care Med. 1999.)
Conclusions

Positive pressure ventilation may injure the lung via several different mechanisms:

- Alveolar distension "VOLUTRAUMA"
- Repeated closing and opening of collapsed alveolar units "ATELECTRAUMA"
- Oxygen toxicity
- Lung inflammation "BIOTRAUMA"
- VILI
- Multiple organ dysfunction syndrome
Recommendations in Practice

- Principle of precaution
- Limited VT 6 mL/kg PBW to avoid alveolar distension
- End-inspiratory plateau pressure < 30 - 32 cm H₂O
- Adequate end-expiratory lung volumes utilizing PEEP and higher mean airway pressures to minimize atelectrauma and improve oxygenation
- Consider recruitment maneuvers
- Avoid oxygen toxicity: FiO₂ < 0.7 whenever possible
- Monitor hemodynamics, mechanics, and gas exchange
- Address deficits of intravascular volume
- Prioritize patient comfort and safety
VILI: Remaining Questions

- Optimal tidal volume, Pplat, PEEP
- Role of recruitment maneuvers
- High-frequency ventilation
- Permissive hypercapnia
- Prone positioning