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Bethesda, MD, USA
Acute Respiratory Failure

• Types of Respiratory Failure
• ARDS
  - Definition
  - Causes and Predisposing Conditions
  - Pathophysiology
  - Clinical Stages and Clinical Features
  - Mechanical Ventilation
  - Innovative and Novel Therapies
  - Summary
Acute Respiratory Failure

- Acute Hypoxemic Failure - Impairment in oxygenation

- Acute Hypercarbic Failure - Impairment in ventilation with hypoxemia and hypercarbia
Acute Hypoxemic Failure - Acute Respiratory Distress Syndrome

• **Acute Lung Injury (ALI):** Acute in onset
  - $\text{PaO}_2/\text{FiO}_2 < 300 \text{ mm Hg}$ (regardless PEEP level)
  - Bilateral infiltrates
  - PAOP $< 18 \text{ mm Hg}$ or no clinical evidence of left atrial hypertension

• **ARDS:** Acute in onset
  - $\text{PaO}_2/\text{FiO}_2 < 200 \text{ mm Hg}$ (regardless PEEP level)
  - Bilateral infiltrates
  - PAOP $< 18 \text{ mm Hg}$ or no clinical evidence of left atrial hypertension

Am J Respir Crit Care Med 1994; 149:818
Clinical Disorders Associated with ARDS

Direct Lung Injury

Common causes
- Pneumonia
- Aspiration

Less common causes
- Pulmonary contusion
- Fat emboli
- Near-drowning
- Inhalational injury
- Reperfusion pulm.edema after lung transplant or pulm. embolectomy

Indirect Lung Injury

Common causes
- Sepsis
- Severe trauma with shock and multiple transfusions

Less common causes
- Cardiopulm bypass
- Drug overdose
- Acute pancreatitis
- Transfusion of blood products
Factors that Increase ARDS Risk

- Age
- Female gender (trauma only)
- Genetic Factors
- Severity of illness
  - Acute Physiology and Chronic Health Evaluation (APACHE) III
- Cigarette smoking
- Chronic alcohol abuse
- Combination of risk factors
Pathogenesis

- Two layers lead to alveolar-capillary barrier
  - microvascular endothelium
  - alveolar epithelium

- **Acute phase of ALI/ARDS:**
  Influx of protein-rich edema fluid into air spaces due to increased permeability of the alveolar-capillary barrier
Pathogenesis

Later development of interstitial edema: The quantity of fluid pouring from the capillaries overwhelms the capacity of the interstitium and the lymphatics, resulting in interstitial edema. Arrows represent lymphatic movement; small circles represent protein.

Development of alveolar edema: Breakdown of the alveolar epithelial barrier allows leakage of edema fluid into the alveolar space. Arrows represent lymphatic movement; small circles represent protein.
The Normal Alveolus (Left-Hand Side) and the Injured Alveolus in the Acute Phase of Acute Lung Injury and the Acute Respiratory Distress Syndrome (Right-Hand Side)

ARDS - Histology

Normal Lung

Diffuse Alveolar Damage

Diffuse Alveolar Damage
Findings on Light Microscopy and Electron Microscopy during the Acute Phase (Panels A and D) and the Fibrosing-Alveolitis Phase (Panels B, C, and E) of Acute Lung Injury and the Acute Respiratory Distress Syndrome

Radiographic and Computed Tomographic (CT) Findings in the Acute, or Exudative, Phase (Panels A and C) and the Fibrosing-Alveolitis Phase (Panels B and D) of Acute Lung Injury and the Acute Respiratory Distress Syndrome

Physiologic Derangements

• **Impaired Gas Exchange:**
  
  Physiologic shunting Ventilation/Perfusion mismatch are the major causes of hypoxemia

• **Decreased Lung Compliance:**
  
  One of the hallmarks of ARDS. Decreased compliance is due to stiffness of poorly aerated lung and to a smaller extent on pressure-volume characteristics of residual functioning units

• **Pulmonary Hypertension:** seen in about 25% of ARDS pts on mech.vent. It is due to hypoxic vasoconstriction and vascular compression by positive pressure ventilation
Clinical Stages of ARDS

• **Exudative Stage**: Diffuse Alveolar damage (DAD)

• **Proliferative Stage**: There is resolution of pulmonary edema, proliferation of type II alveolar cells, squamous metaplasia, interstitial infiltration by myofibroblasts and early deposition of collagen

• **Fibrotic Stage**: Some patients progress to this stage in which there is obliteration of normal lung architecture, diffuse fibrosis and cyst formation
Clinical Features in ARDS - Early Stage

- Early Stage: day 1-7
  - Clinical features of underlying disease
  - Then rapidly developing worsening of tachypnea, dyspnea and hypoxemia (severe)
- Lab findings are not specific for ARDS.
Clinical Features in ARDS - Proliferative day 7-21

• In the first week, resolution of pulmonary edema occurs. Oxygenation may improve.

• Majority of patients require mechanical ventilation due to continued hypoxemia and high minute ventilation (poor lung compliance).

• Complication such as barotrauma, nosocomial infection and multi-organ system failure occur.
Clinical Features in ARDS - Late Stage day >21

- In late stages, difficulty in oxygenation is due to:
  - large dead space ventilation
  - high minute ventilation requirement
  - surfactant dysfunction.

- Fibrosis may occur:
  - ↑ in airway pressure
  - progressive pul. HTN
  - honeycomb changes on CXR
ARDS Treatment

- Mechanical ventilation
- Treatment of underlying etiology
- Other supportive measures
Mechanical Ventilation

• Most important treatment modality for ARDS

• Mechanical ventilation provides:
  - reliable oxygen supplementation
  - decreased work of breathing
  - decreased venous return leading to decrease in transvascular hydrostatic pressure and edema formation
  - recruitment of atelectatic lung units
Mechanical Ventilation - Goal

- Effective ventilator strategy is aimed to achieve adequate oxygenation with FiO2 less than 50-60%

- Select appropriate level of PEEP and a safe mode of ventilation to
  - augment gas exchange
  - limit ventilator-associated lung injury (micro and macro barotrauma)
**Macrobarotrauma**
- Pneumothorax
- Interstitial emphysema
- Subcutaneous emphysema
- Pneumomediastinum
- Air embolism
- 13% suffered barotrauma. Only 2% contributed to mortality
- Higher levels of PEEP is a risk factor for barotrauma

**Microbarotrauma**
- Less obvious but causes more lung injury
- Overdistension of alveoli $\rightarrow$ microvascular injury and high permeability edema
- Low tidal volume ventilation showed significantly lower mortality
Barotrauma

Bilateral pneumothoraces  Patient with ARDS, increased permeability pulmonary edema, and barotrauma. Supine chest radiograph shows right subpulmonic and left apicolateral pneumothorax. Streaky lucencies are permeating the otherwise consolidated lungs as a reflection of interstitial pulmonary emphysema. The patient has a tracheostomy tube in place with a markedly hyperexpanded cuff, due to tracheomalacia. Courtesy of Paul Stark, MD.

Soft tissue emphysema following alveolar disruption  Air from torn alveolus first enters perivascular interstitium (A), dissecting proximally within the bronchovascular sheath toward the mediastinum (B). As airway pressure rises, decompression occurs into cervical (C), subcutaneous (D), and pericardial (E) tissue spaces. Pleural rupture may result in pneumothorax (F). Small arrows indicate the direction of air movement. (Redrawn from Maunder RJ, Pierson DJ, Hudson LD, Arch Intern Med 1984; 144:1449.)
Effect of Atelectactic Units

**Shear forces** When lung units collapse, they may stretch adjacent, non-atelectatic lung units and create damaging shear forces.
Pressure-Volume Curve in ARDS

Pressure-volume relationships during mechanical ventilation

Pressure-volume curve in ARDS: Pressure-volume curve in a patient with acute respiratory distress syndrome (ARDS). The deflection point indicates a change in the slope of the curve, suggesting a transition in the mechanical properties of the lungs.
Mode of Ventilation: Volume Cycled versus Pressure Controlled Ventilation

Volume-cycled

Advantages
- Guaranteed tidal volume (TV) and minute ventilation (VE)
- Clinician familiarity

Disadvantages
- Airway pressure not controlled
- Worse patient tolerance

Pressure controlled

Advantages
- Airway pressure controlled
- Patient tolerance

Disadvantages
- Less clinician familiarity
- TV and VE not guaranteed
Positive End Expiratory Pressure (PEEP) in ARDS

- Increased end expiratory volume
- Recruitment of unventilated alveoli
- Decreased perfusion of unventilated alveoli
- Improvement in V/Q matching
- Decreased intrapulmonary shunt

### Arterial oxygenation and PEEP

Oxygenation goal PaO2 55–80 mmHg or SpO2 88–95 percent

Use these FiO2/PEEP combinations to achieve oxygenation goal:

<table>
<thead>
<tr>
<th>FiO2</th>
<th>0.3</th>
<th>0.4</th>
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<tr>
<td>PEEP</td>
<td>5</td>
<td>5–8</td>
<td>8–10</td>
<td>10</td>
<td>10–14</td>
<td>14</td>
<td>14–18</td>
<td>18–22</td>
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PEEP should be applied starting with the minimum value for a given FiO2.
Low Tidal Volume Ventilation

- Animal experiments with normal lungs showed alveolar overdistension causes microbarotrauma to vessels (VILI)
- Adults: initiate TV at 6-8 ml/Kg
- Low TV ventilation reduces ventilator associated lung injury (VALI)
Mean (SE) Mortality Rate among 257 Patients with Acute Lung Injury and the Acute Respiratory Distress Syndrome Who Were Assigned to Receive Traditional Tidal Volumes and 260 Such Patients Who Were Assigned to Receive Lower Tidal Volumes, According to the Quartile of Static Compliance of the Respiratory System before Randomization
# Outcome Variables Lower vs Traditional TV

## Table 4. Main Outcome Variables.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group Receiving Lower Tidal Volumes</th>
<th>Group Receiving Traditional Tidal Volumes</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>

ARDSnet Trial Recommendations

- Calculate predicted body weight
- Set mode to assist control
- Start with 8ml/kg TV & ↓ it to 6 ml/kg in 1-3 h
- Set initial rate to <35/mt to match baseline VE
- Plateau pressure (Pplat) goal is <30 mmH$_2$O

**Arterial oxygenation and PEEP**

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PEEP should be applied starting with the minimum value for a given FiO2.
Treatment of ARDS - Other Strategies

- Use of sedatives and analgesics
- Prone position
- Other modes of ventilation such as inverse ratio, Pressure release ventilation, high frequency ventilation, liquid ventilation, extracorporeal membrane oxygenator
- Pharmacologic interventions
Sedatives and Analgesics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial dose</th>
<th>Maintenance dosage</th>
<th>Peak, min</th>
<th>Duration after bolus, min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl</td>
<td>25-100 mcg</td>
<td>0.5-2 mcg/kg/h</td>
<td>2-5</td>
<td>30-45</td>
</tr>
<tr>
<td>Morphine</td>
<td>2-5 mg</td>
<td>2-10 mg/h</td>
<td>30</td>
<td>120-240</td>
</tr>
<tr>
<td>Midazolam</td>
<td>0.5-2 mg</td>
<td>0.01-0.2 mg/kg/h</td>
<td>2-5</td>
<td>30-120</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>0.5-2 mg</td>
<td>0.01-0.1 mg/kg/h</td>
<td>15-30</td>
<td>360-480</td>
</tr>
<tr>
<td>Propofol</td>
<td>0.5 mg/kg</td>
<td>5-75 mcg/kg/min</td>
<td>&lt;1</td>
<td>5-10</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>2-10 mg</td>
<td>25% of load q6 hrs</td>
<td>30</td>
<td>Variable (hours)</td>
</tr>
</tbody>
</table>
Prone Positioning of Patient

- Re-expansion of gravity induced atelectasis
- Improvement of V/Q matching
- Increased FRC
- Mobilization of secretions
Prone Position:

**Contraindications**
- Shock
- Acute bleeding
- Multiple trauma
- Spinal instability
- Pregnancy
- ↑ intracranial pressure
- Abdominal surgery

**Complications**
- Nerve compression
- Crush injury
- Venous stasis
- Airway security
- Diaphragm limitation
- Pressure sores
- Dislodging vascular cath
- Retinal damage

Ryan DW; Pelosi, P BMJ 1996; 312:860
Inhaled Nitric Oxide (NO) in ARDS

Oxygenation improves. But no benefit in number days on mechanical ventilation or mortality with use of NO.
Liquid Ventilation in ARDS

• Ventilation with perfluorocarbon liquids
• Partial or total liquid ventilation
• Perfluorocarbon liquid evaporates
• No benefit over traditional ventilation in ARDS
High Frequency Ventilation
Extracorporeal Oxygenation

Membrane oxygenator in use. These devices can provide continuous extracorporeal oxygenation and carbon dioxide removal for several weeks. Courtesy of Charles Marquette, MD.
Results of Clinical Trials of Pharmacologic Treatment for Acute Lung Injury and the Acute Respiratory Distress Syndrome

- Glucocorticoids in early stage - no benefit
- Alprostadil - no benefit
- Surfactant - no benefit in adults
- Inhaled nitric oxide - no benefit
- Ketoconazole - no benefit
- Procysteine - lack of efficacy
- Lysofylline - lack of efficacy
- Glucocorticoids in late stages - beneficial
Predictors of mortality

- APACHE Score
- SAPS
- Dead Space ventilation at time of presentation
Prognosis of ARDS

• In the first 2-3 days, underlying etiology
• Nosocomial infection, barotrauma
• Late stages: progressive pulmonary fibrosis

• Survivors of ARDS: May have normal lung function, some have mild to modest pulmonary function limitation. Few have severe pulmonary impairment
Acute Respiratory Failure - ARDS

Summary

• Mechanical ventilation is critical
• Low tidal volume ventilation is associated with less VALI
• Survival benefit is seen with LTV ventilation
• PEEP improves oxygenation
• In late stages corticosteroids may benefit
• HFV shows promise for adults
The Normal Alveolus (Left-Hand Side) and the Injured Alveolus in the Acute Phase of Acute Lung Injury and the Acute Respiratory Distress Syndrome (Right-Hand Side)

Survival and Discharge to Home by Treatment

Days After Randomization

- 6 ml/kg Survival
- 12 ml/kg Survival
- 6 ml/kg Discharge
- 12 ml/kg Discharge

Brower, R. G. et al. Chest 2001;120:1347-1367
ARDS - Common Causes

- Sepsis
- Aspiration
- Infectious pneumonia
- Severe trauma
- Burns
- Multiple blood transfusions
- Leukoagglutinin reactions
- Drug overdose
- Near drowning
- Smoke inhalation
- Acute Eosinophilic P
- Pancreatitis
- Cardiopulmonary bypass
- Pulmonary contusion
- Multiple fractures
- Following UAO obstruction
- BOOP
- Bone marrow transplant
- Drug reaction
- Air embolism
- Amniotic fluid embolism
- Miliary TB
Pressure volume curves with positive pressure ventilation. Pressure-volume curves in two patients, each with three sets of curves at 0, 10, and 20 cmH2O PEEP. In each instance the lower limb represents the inflation curve and the upper limb represents the deflation curve of the lung at each setting of PEEP. The patient on the left was receiving mechanical ventilation for coma. At each level of PEEP, there is an immediate and steep ascent of volume recruited as transpulmonary pressure increases. Towards higher pulmonary pressures at a level of 20 cmH2O PEEP, the slope of the curve flattens as the deflection point of the pressure-volume curve has been attained; additional volume does not occur at higher airway pressures, suggesting overdistension of the lung. The patient on the right was ventilated for ARDS. The significant differences between the inflation (lower limb) and deflation (higher limb) curves in this patient represent the phenomenon known as hysteresis. The gap is narrowed at higher (20 cmH2O) levels of PEEP. Thus, PEEP helps to minimize hysteresis in patients with ARDS, making the curve appear more those in the patient on the left without ARDS. Without PEEP, the inflation limb (green curve) is flat between 0 and 10 cmH2O, indicating little alveolar recruitment at these low levels of airway pressure. This flattened slope is less apparent at 10 cmH2O PEEP and absent at 20 cmH2O PEEP due to the beneficial effects of PEEP in ARDS in increasing end-expiratory lung volume. At 20 cmH2O PEEP, the slope once again flattens at high airway pressures, just as in the patient without ARDS, again suggesting overdistension of lung units. (Redrawn from Bon Toro, Lemaire, J Crit Care Med 1990; 5:27)
**Volume Cycled versus Pressure Controlled Ventilation**

**Volume cycled**

**Advantages**
- Guaranteed tidal volume and VE
- Clinician familiarity

**Disadvantages**
- Airway pressures not controlled
- Worse patient tolerance

**Pressure controlled**

**Advantages**
- Airway pressures controlled
- Better patient tolerance

**Disadvantages**
- Less clinician familiarity
  - VT and VE not guaranteed
How PEEP Improves Oxygenation in ARDS

- Increased end-expiratory lung volume
- Recruitment of unventilated alveoli
- Decreased perfusion of unventilated alveoli
- Improvement in V/Q matching
- Decreased intrapulmonary shunt
Prone Position: Rationale

- Reexpansion of gravity-induced atelectasis
- Improvement of V/Q matching
- Increased FRC
- Mobilization of secretions
**Pressure controlled inverse ratio ventilation** Depiction of flow and airway pressure characteristics during a pressure limited breath provided by pressure-controlled inverse ratio ventilation (PC-IRV). End-expiratory alveolar pressure is positive at the end of the shortened expiratory period. Airflow has not ceased, and auto-PEEP has developed. A pressure limited breath without inverse ratio ventilation has similar pressure and flow characteristics except that flow has ceased at the end of expiration, and there is no auto-PEEP present. (Redrawn from Marcy, TW, Marini, JJ, Chest 1991; 100:494).
**Volume-controlled inverse ratio ventilation** Depiction of flow, airway, and alveolar pressures during three forms of volume-controlled inverse ratio ventilation (VC-IRV): slow inspiratory flow; constant flow with an end-inspiratory pause; and decelerating flow. Airway pressures are indicated by the thick line. Alveolar pressure during the respiratory cycle is indicated by the shaded area. For equivalent tidal volume, frequency, and I:E ratio, a constant flow with an end-inspiratory pause has the highest mean airway pressure. As during pressure controlled-IRV, expiratory flow and positive alveolar pressure (auto-PEEP) are present at the end of the expiratory phase. (Redrawn from Marcy, TW, Marini, JJ, Chest 1991; 100:494.)
Gas transport mechanisms during high-frequency ventilation. The major gas transport mechanisms that are operative under physiologic conditions in each region (convection, convection and diffusion, and diffusion alone) are shown. There are seven potential mechanisms that can enhance gas transport during high-frequency ventilation: turbulence in the large airways, causing enhanced mixing; direct ventilation of close alveoli; turbulent flow with lateral convective mixing; pendelluft (asynchronous flow among alveoli due to asymmetries in airflow impedance); gas mixing due to velocity profiles that are axially asymmetric (leading to the streaming of "fresh" gas toward the alveoli along the inner wall of the airway and the streaming of "alveolar" gas away from the alveoli along the outer wall); laminar flow with lateral transport by diffusion (Taylor dispersion); and collateral ventilation through nonairway connections between neighboring alveoli. Reproduced with permission from Slutsky, AS, Brazen, JM. Ventilation with small tidal volumes. N Engl J Med 2002; 347:631. Copyright © 2002 Massachusetts Medical Society.
Protocol for Jet Ventilator Settings

- Driving pressure of 35 psi
- Inspiratory time of 30 percent
- Frequency of 150 breaths per minute
- FiO2 of 1.0
- PEEP of 0 cmH2O or equal to that used during conventional ventilation

Check arterial blood gas in 15 minutes

Is the PaCO2 appropriate?

If hypercapnic:
- Increase driving pressure by 5-psi increments up to maximum of 50 psi
- Increase inspiratory time in 5 percent increments up to maximum of 40 percent
- Increase frequency in 10 breaths/minute increments up to maximum of 250
- Can add conventional tidal volume breaths or pressure support

If hypocapnic:
- Decrease driving pressure by 5-psi decrements
- Decrease inspiratory time by 5 percent decrements to minimum of 20 percent
- Decrease frequency in 10-breaths/minute decrements to minimum of 100

Is the PO2 appropriate?

If hypoxic:
- Add PEEP in 3-cmH2O to 5-cmH2O increments
- Increase driving pressure by 5-psi increments up to maximum of 50 psi
- Increase inspiratory time in 5 percent increments up to maximum of 40 percent

If hypoxic:
- Decrease FiO2
- Decrease PEEP if present
# History of Alternative Ventilatory Strategies for Acute Lung Injury and the Acute Respiratory Distress Syndrome

## Table 3. History of Alternative Ventilatory Strategies for Acute Lung Injury and the Acute Respiratory Distress Syndrome.

<table>
<thead>
<tr>
<th>Ventilatory Strategy</th>
<th>Year</th>
<th>Type of Study</th>
<th>No. of Patients</th>
<th>Findings</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>High levels of positive end-expiratory pressure</td>
<td>1975</td>
<td>Observational</td>
<td>28</td>
<td>High incidence of pneumothorax</td>
<td>Kirby et al.94</td>
</tr>
<tr>
<td>Extracorporeal membrane oxygenation</td>
<td>1979</td>
<td>Phase 3 multicenter trial</td>
<td>90</td>
<td>No benefit</td>
<td>Zapol et al.93</td>
</tr>
<tr>
<td>High-frequency jet ventilation</td>
<td>1983</td>
<td>Phase 3 single-center trial</td>
<td>309</td>
<td>No benefit</td>
<td>Carlon et al.95</td>
</tr>
<tr>
<td>Prophylactic positive end-expiratory pressure (8 cm of water)</td>
<td>1984</td>
<td>Phase 3 single-center trial</td>
<td>92</td>
<td>No benefit in patients at risk for the acute respiratory distress syndrome</td>
<td>Pepe et al.96</td>
</tr>
<tr>
<td>Pressure-controlled inverse-ratio ventilation</td>
<td>1994</td>
<td>Observational</td>
<td>9</td>
<td>Inconclusive, needs further study</td>
<td>Lessard et al.97</td>
</tr>
<tr>
<td>Extracorporeal removal of carbon dioxide</td>
<td>1994</td>
<td>Phase 3 single-center trial</td>
<td>40</td>
<td>No benefit</td>
<td>Morris et al.98</td>
</tr>
<tr>
<td>Liquid ventilation</td>
<td>1996</td>
<td>Observational</td>
<td>10</td>
<td>Probably safe, needs further study</td>
<td>Hirschl et al.99</td>
</tr>
<tr>
<td>High-frequency oscillatory ventilation</td>
<td>1997</td>
<td>Observational</td>
<td>17</td>
<td>Probably safe, needs further study</td>
<td>Fort et al.100</td>
</tr>
<tr>
<td>Prone positioning during ventilation</td>
<td>1997</td>
<td>Observational</td>
<td>13</td>
<td>Inconclusive, needs further study</td>
<td>Mure et al.101</td>
</tr>
<tr>
<td>Prone positioning during ventilation “Open-lung” approach</td>
<td>2000</td>
<td>Observational</td>
<td>39</td>
<td>Inconclusive, needs further study</td>
<td>Nakos et al.102</td>
</tr>
<tr>
<td>Low tidal volumes</td>
<td>1998</td>
<td>Phase 3</td>
<td>120</td>
<td>No benefit in patients at risk for the acute respiratory distress syndrome</td>
<td>Stewart et al.104</td>
</tr>
<tr>
<td>Low tidal volumes</td>
<td>1998</td>
<td>Phase 3</td>
<td>116</td>
<td>No benefit</td>
<td>Brochard et al.105</td>
</tr>
<tr>
<td>Low tidal volumes</td>
<td>2000</td>
<td>Phase 3</td>
<td>861</td>
<td>Decreased mortality by 22 percent (as compared with traditional tidal volumes)</td>
<td>Acute Respiratory Distress Syndrome Network106</td>
</tr>
</tbody>
</table>

*Ware, L. B. et al. N Engl J Med 2000;342:1334-1349*
**Ventilator Management in Patients with Acute Respiratory Distress Syndrome or Acute Lung Injury†**

**Initial ventilator settings**

Calculate predicted body weight (PBW)

- **Male** = 50 + 2.3 \[\text{height (inches)} - 60\] **OR**
  50 + 0.91 \[\text{height (cm)} - 152.4\]
- **Female** = 45.5 + 2.3 \[\text{height (inches)} - 60\] **OR**
  45.5 + 0.91 \[\text{height (cm)} - 152.4\]

Set mode to volume assist-control

- Set initial tidal volume to 8 ml/kg PBW
- Reduce tidal volume to 7 and then to 6 ml/kg over 1-3 hours

Set initial ventilator rate ≤ 35 breaths/min to match baseline minute ventilation

**Subsequent tidal volume adjustment**

Plateau pressure (Pplat) goal ≤ 30 cmH2O

Check inspiratory plateau pressure with 0.5 second inspiratory pause at least every four hours and after each change in PEEP or tidal volume.

- If Pplat > 30 cmH2O, decrease tidal volume in 1 ml/kg PBW steps to 5 or if necessary to 4 mL/kg PBW.

- If Pplat < 25 cmH2O and tidal volume < 6 ml/kg, increase tidal volume by 1 mL/kg PBW until Pplat > 25 cmH2O or tidal volume = 6 ml/kg.

- If breath stacking (autoPEEP) or severe dyspnea occurs, tidal volume may be increased to 7 or 8 mL/kg PBW if Pplat remains ≤ 30 cmH2O.

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<tr>
<td>PEEP</td>
<td>5</td>
<td>5-8</td>
<td>8-10</td>
<td>10</td>
<td>10-14</td>
<td>14</td>
<td>14-18</td>
<td>18-22</td>
</tr>
</tbody>
</table>

PEEP should be applied starting with the minimum value for a given FiO2.

Declining mortality rates in ARDS Data from the University of Washington demonstrating decreasing mortality among ARDS patients during the early 1990's. (Redrawn from Milberg, JA, Davis, DR, Steinberg, KP, et al. JAMA 1995; 273:306.)
Effects of inhaled prostacyclin and inhaled nitric oxide on pulmonary hemodynamics. The approximately equivalent efficacy of inhaled prostacyclin (PGI2) and inhaled nitric oxide (NO) was demonstrated in eight patients with severe ARDS who were treated sequentially with both agents. (Redrawn from Zwissler, B, Kemming, G, Habler, O, et al, Am J Respir Crit Care Med 1996; 154:1671.)
**Benefit of APRV in ARDS** Changes over time in alveolar-arterial gradient divided by the fraction of the oxygen concentration (A-aO2/FiO2) in mmHg in patients with ARDS who were treated either by volume-controlled cycled inverse ratio ventilation (VC-IRV; blue squares) or airway pressure release ventilation (APRV; red circles) during a 24 hour period. There is additional alveolar recruitment by 16 hours in the APRV group as reflected by a significant decrease in A-aO2/FiO2. This improvement persisted at 24 hours. Similar results (not shown) were obtained for changes in shunt fraction with APRV at 16 and 24 hours when compared to VC-IRV. ** p<0.005 compared with value at onset of APRV; $ p<0.05; $$ p<0.01 comparing VC-IRV and APRV. (Adapted from Sydow, M. Burchardi, H, Ephraim, et al, Am J Respir Crit Care Med 1994; 149:1550.)
Airway pressure release (APR) ventilation

A. Continuous flow CPAP.

B. During exhalation with CPAP, the CPAP valve opens and the APR valve closes.

C. During airway pressure release from the preset CPAP level to ambient pressure, the CPAP valve closes and the APR valve opens. After closure of the APR valve, FRC is re-established. (Adapted from Downs, JB, Stock, MC, Crit Care Med 1987; 15:459.)
<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>GROUP RECEIVING LOWER TIDAL VOLUMES</th>
<th>GROUP RECEIVING TRADITIONAL TIDAL VOLUMES</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>

*Plus–minus values are means ±SD. The number of ventilator-free days is the mean number of days from day 1 to day 28 on which the patient had been breathing without assistance for at least 48 consecutive hours. Barotrauma was defined as any new pneumothorax, pneumomediastinum, or subcutaneous emphysema, or a pneumatocele that was more than 2 cm in diameter. Organ and system failures were defined as described in the Methods section.*
Clinical Disorders Associated with the Development of the Acute Respiratory Distress Syndrome

**Table 2. Clinical Disorders Associated with the Development of the Acute Respiratory Distress Syndrome.**

<table>
<thead>
<tr>
<th><strong>Direct Lung Injury</strong></th>
<th><strong>Indirect Lung Injury</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common causes</strong></td>
<td><strong>Common causes</strong></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Sepsis</td>
</tr>
<tr>
<td>Aspiration of gastric contents</td>
<td>Severe trauma with shock and multiple transfusions</td>
</tr>
<tr>
<td><strong>Less common causes</strong></td>
<td><strong>Less common causes</strong></td>
</tr>
<tr>
<td>Pulmonary contusion</td>
<td>Cardiopulmonary bypass</td>
</tr>
<tr>
<td>Fat emboli</td>
<td>Drug overdose</td>
</tr>
<tr>
<td>Near-drowning</td>
<td>Acute pancreatitis</td>
</tr>
<tr>
<td>Inhalational injury</td>
<td>Transfusions of blood products</td>
</tr>
<tr>
<td>Reperfusion pulmonary edema after lung transplantation or pulmonary embolectomy</td>
<td></td>
</tr>
</tbody>
</table>

- Ventilation with perfluorocarbon liquids
- Partial or total liquid ventilation
- Perfluorocarbon liquid evaporates

**PHYSICAL PROPERTIES OF PERFLUBRON**

<table>
<thead>
<tr>
<th></th>
<th>Perflubron</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Density (g/mL; at 25'C)</td>
<td>1.93</td>
<td>1</td>
</tr>
<tr>
<td>Vapor pressure (torr; at 37'C)</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Surface tension (dynes/cm; at 25'C)</td>
<td>18</td>
<td>75</td>
</tr>
<tr>
<td>Oxygen solubility (mL / 100 mL; at 25'C)</td>
<td>53</td>
<td>2</td>
</tr>
<tr>
<td>Carbon dioxide solubility (mL / 100 mL; at 37'C)</td>
<td>210</td>
<td>70</td>
</tr>
</tbody>
</table>