Seminar
Current Concepts
In ARDS
What I think is possible to cover in 40 minutes:

- Definition

- Management
  - Ventilatory strategies
    - Conventional LPV
    - Rescue therapy
  - Non Ventilatory strategies
Definition and Diagnosis

• First described by Ashbaugh and Petty-1967

• Case series of 12 patients


• No valid definition for almost 25 years
Definition and Diagnosis contd..

- In 1994 AECC definition of ARDS
- Four key features
  - Acute
  - Hypoxemia
  - CXR
  - Non cardiogenic nature
- Broader term ALI- to include less severe disease

Definition and Diagnosis contd..

Why new definition is required?

1. What is acute?

2. Does PEEP affect P/F ratio?

3. CXR- Subjective- Can it be made more objective?

4. Requires RHC!!!

• Term ALI- “Exclusive” or “Inclusive”

• No severity stratification for ARDS

Definition and Diagnosis contd..

- ESICM with endorsement from ATS & Society of Critical Care Medicine – Convened an International expert panel
- First meeting in Berlin from Sep 30th to Oct 2nd 2011-Draft definition of ARDS
- Evaluated on 4000 patients of presumed ARDS for ability to predict short term mortality

Definition and Diagnosis contd..

**Figure. Outline of Consensus Process**

- **Premeeting preparations (May to September 2011)**
  - Selection of panelists by chairs
  - Precirculation of key topics for discussion
  - Preparation of background material by panelists

- **In-person discussions (September 30 to October 2, 2011, Berlin, Germany)**
  - Presentations of key background material
  - Development of the conceptual model of ARDS
  - Draft of Berlin Definition based on informal consensus discussions

- **Empirical evaluation of draft definition (October 2011 to January 2012)**
  - Assembling clinical and physiologic cohorts
  - Demonstration of patient characteristics and distribution according to definition categories
  - Evaluation of impact of ancillary variables for severe ARDS subgroup

- **Follow-up of consensus discussions and analysis (February 2012 by multiple teleconferences)**
  - Presentation of empirical evaluation
  - Final definition created based on further informal consensus discussions
  - Decision to present the results of a post hoc higher-risk subset
  - Testing of predictive validity

ARDS indicates acute respiratory distress syndrome.

**Definition and Diagnosis contd..**

**Table 3. The Berlin Definition of Acute Respiratory Distress Syndrome**

<table>
<thead>
<tr>
<th>Timing</th>
<th>Within 1 week of a known clinical insult or new or worsening respiratory symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest imaging&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Bilateral opacities—not fully explained by effusions, lobar/lung 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 (eg, echocardiography) to exclude hydrostatic edema if no risk factor present</td>
</tr>
<tr>
<td>Oxygenation&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>200 mm Hg &lt; Pao&lt;sub&gt;2&lt;/sub&gt; / FiO&lt;sub&gt;2&lt;/sub&gt; ≤ 300 mm Hg with PEEP or CPAP ≥5 cm H&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;C&lt;/sub&gt;</td>
</tr>
<tr>
<td>Moderate</td>
<td>100 mm Hg &lt; Pao&lt;sub&gt;2&lt;/sub&gt; / FiO&lt;sub&gt;2&lt;/sub&gt; ≤ 200 mm Hg with PEEP ≥5 cm H&lt;sub&gt;2&lt;/sub&gt;O</td>
</tr>
<tr>
<td>Severe</td>
<td>Pao&lt;sub&gt;2&lt;/sub&gt; / FiO&lt;sub&gt;2&lt;/sub&gt; ≤ 100 mm Hg with PEEP ≥5 cm H&lt;sub&gt;2&lt;/sub&gt;O</td>
</tr>
</tbody>
</table>

Abbreviations: CPAP, continuous positive airway pressure; FiO<sub>2</sub>, fraction of inspired oxygen; Pao<sub>2</sub>, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure.

<sup>a</sup>Chest radiograph or computed tomography scan.

<sup>b</sup>If altitude is higher than 1000 m, the correction factor should be calculated as follows: \([\text{Pao}_2/\text{FiO}_2 \times (\text{barometric pressure}/760)]\).

<sup>c</sup>This may be delivered noninvasively in the mild acute respiratory distress syndrome group.

### Table 2. Exploration of Proposed Variables to Define Severe ARDS\(^a\)

<table>
<thead>
<tr>
<th>Severe ARDS Definition</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%) of Patients</td>
<td>% Mortality (95% CI)</td>
<td>No. (%) of Patients</td>
</tr>
<tr>
<td>Consensus panel draft</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\text{Pa}_2/\text{Fi}_O_2 \leq 100 \text{ mm Hg} + )</td>
<td>220 (22)</td>
<td>27 (24-30)</td>
<td>2344 (84)</td>
</tr>
<tr>
<td>chest radiograph of 3 or 4 quadrants +</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEEP (\geq 10 \text{ cm H}<em>2\text{O} + (\text{C}</em>{R_{es}} \leq 40 \text{ mL/cm} \text{H}_2\text{O} )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>or (\text{VE}_{corr} \geq 10 \text{ L/min})</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consensus panel final</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\text{Pa}_2/\text{Fi}_O_2 \leq 100 \text{ mm Hg})</td>
<td>220 (22)</td>
<td>27 (24-30)</td>
<td>1820 (50)</td>
</tr>
</tbody>
</table>

Abbreviations: ARDS, acute respiratory distress syndrome; \(\text{C}_{R_{es}}\), compliance of the respiratory system; \(\text{Fi}_O_2\), fraction of inspired oxygen; \(\text{Pa}_2\), arterial partial pressure of oxygen; PEEP, positive end-expiratory pressure; \(\text{VE}_{corr}\), corrected expired volume per minute.

\(^a\)The moderate group includes patients with \(\text{Pa}_2/\text{Fi}_O_2 \leq 200 \text{ mm Hg}\) and patients with \(\text{Pa}_2/\text{Fi}_O_2 \leq 100 \text{ mm Hg}\) who do not meet the additional criteria for severe ARDS in the draft definition. All patients are receiving at least 5 cm H\(_2\)O PEEP and have bilateral infiltrates on chest radiograph.

\(^b\)\(^P\leq .001\) comparing mortality across stages of ARDS (mild, moderate, severe) for draft and final definitions.

\(^c\)\(^P = .97\) comparing mortality in consensus draft severe ARDS to consensus final severe ARDS definitions.

To conclude -

<table>
<thead>
<tr>
<th></th>
<th>AECC</th>
<th>Berlin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration</td>
<td>Vague</td>
<td>1 week</td>
</tr>
<tr>
<td>P/F ratio</td>
<td>&lt;200</td>
<td>&lt;300</td>
</tr>
<tr>
<td>Requires</td>
<td>RHC</td>
<td>Ventilator</td>
</tr>
<tr>
<td>Conceptually</td>
<td>Conservative/Restrictive</td>
<td>More liberal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>“INCLUSIVE”</td>
</tr>
</tbody>
</table>

Possibly both are complimentary to each other
Current in Ventilatory strategies -

- Conventional LPV
- Unconventional
  - Higher PEEP
  - Recruitment
  - PCIRV
  - APRV
  - HFOV
Dawn of LTVV/LPV
### 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>

*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.
Does compliance at baseline predict response to LTV?

**Figure 2.** 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.

The interaction between the study group and the quartile of static compliance at baseline was not significant (P=0.49).

*New Engl j of med* 2000;342(18):1301-8
• What does literature say about long term effects of LTVV
Lung protective mechanical ventilation and two year survival in patients with acute lung injury: prospective cohort study

Dale M Needham associate professor\(^1\)\(^2\), Elizabeth Colantuoni assistant scientist\(^3\), Pedro A Mendez-Tellez assistant professor\(^4\), Victor D Dinglas research programme supervisor\(^1\), Jonathan E Sevransky assistant professor\(^1\), Cheryl R Dennison Himmelfarb associate professor\(^5\), Sanjay V Desai assistant professor\(^1\), Carl Shanholtz associate professor\(^7\), Roy G Brower professor\(^1\), Peter J Pronovost professor\(^4,5,6\)

Results 485 patients contributed data for 6240 eligible ventilator settings, as measured twice daily (median of eight eligible ventilator settings per patient; 41% of which adhered to lung protective ventilation). Of these patients, 311 (64%) died within two years. After adjusting for the total duration of ventilation and other relevant covariates, each additional ventilator setting adherent to lung protective ventilation was associated with a 3% decrease in the risk of mortality over two years (hazard ratio 0.97, 95% confidence interval 0.95 to 0.99, P=0.002). Compared with no adherence, the estimated absolute risk reduction in two year mortality for a prototypical patient with 50% adherence to lung protective ventilation was 4.0% (0.8% to 7.2%, P=0.012) and with 100% adherence was 7.8% (1.6% to 14.0%, P=0.011).
• Does this mean we are able to save additional approximately 8.8% of ARDS patients, by resorting to LTVV?

• NO
**Outcome - Then And Now**

<table>
<thead>
<tr>
<th>Study period</th>
<th>Valta et al. [8]</th>
<th>Luhr et al. [9]</th>
<th>Bersten et al. [23]</th>
<th>Rubenfeld et al. [10]</th>
<th>Linko et al. [21]</th>
<th>Li et al. [22]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>Retrospective</td>
<td>Prospective</td>
<td>Prospective</td>
<td>Prospective</td>
<td>Prospective</td>
<td>Prospective</td>
</tr>
<tr>
<td>Age, years (mean ± SD or median)</td>
<td>45 ± 2</td>
<td>61 ± 16</td>
<td>62 ± 18</td>
<td>Not reported</td>
<td>61 (50–72)</td>
<td>64 (51–80)</td>
</tr>
<tr>
<td>Tidal volume (ml/kg BW)</td>
<td>8.2 ± 0.4 (measured BW)</td>
<td>8.3 ± 2.7 (measured BW)</td>
<td>9.7 ± 1.9 (measured BW)</td>
<td>Not reported, 10.2 ± 2.6 (from Ref. [10])</td>
<td>8.6 (7.3–9.9) (predicted BW)</td>
<td>Not reported</td>
</tr>
<tr>
<td>PEEP (cmH₂O)</td>
<td>7.8 ± 0.6 (estimated by us)</td>
<td>6.1 ± 3.3</td>
<td>6.3 ± 2.8</td>
<td>Not reported</td>
<td>8 (6–10)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Plateau pressure (cmH₂O)</td>
<td>Not reported</td>
<td>Not reported</td>
<td>25 ± 6.6</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>PaO₂/FiO₂ (mmHg)</td>
<td>123 ± 7</td>
<td>130 ± 37</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Pneumothorax after initiating MV (%)</td>
<td>12</td>
<td>Not reported</td>
<td>10.1</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>ICU mortality (%)</td>
<td>43</td>
<td>Not reported</td>
<td>30.4</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Hospital mortality, %</td>
<td>42</td>
<td>Not reported</td>
<td>41.1</td>
<td>Not reported</td>
<td>Not reported</td>
<td>45% (in 2008)</td>
</tr>
<tr>
<td>28-day mortality</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>47 (ALI/ARDS)</td>
<td>-</td>
</tr>
<tr>
<td>90-day mortality</td>
<td>41.2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Villar J et al. 2011 The ALIEN study, Intensive Care Med 37:1932–1941
Etiology and Outcomes of Pulmonary and Extrapulmonary Acute Lung Injury/ARDS in a Respiratory ICU in North India

Ritesh Agarwal, DM; Ashutosh N. Aggarwal, DM, FCCP; Dheeraj Gupta, DM, FCCP; Digamber Behera, MD, FCCP; and Surinder K. Jindal, MD, FCCP

...tion was available. All patients received mechanical ventilation (Hamilton Amadeus; Bonaduz, GR, Switzerland) using the protocol followed by the ARDS Network low-tidal volume ventilation strategy using ideal body weight to calculate tidal volumes. However, if plateau pressures (Pplat) exceeded 30 cm H₂O or if the pH decreased to < 7.3, the tidal volumes were increased or the positive end-expiratory pressure (PEEP) was decreased, as applicable. The baseline characteristics such as age and gender, ...
Experience at Our Centre-

Table 3—Risk Factors Affecting Outcome of ALI/ARDS Patients in the RICU (Multivariate Logistic Regression Model)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Survivors (n = 94)</th>
<th>Nonsurvivors (n = 86)</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age,* yr Mean (SD)</td>
<td>41 (19)</td>
<td>45 (18)</td>
<td>1.01 (0.99–1.03)</td>
<td></td>
</tr>
<tr>
<td>Female sex,†</td>
<td>47 (50)</td>
<td>30 (34.9)</td>
<td>0.54 (0.29–0.98)‡</td>
<td>0.49 (0.25–0.94)‡</td>
</tr>
<tr>
<td>ARDSexp patients,†</td>
<td>24 (25.5)</td>
<td>33 (38.4)</td>
<td>1.82 (0.96–3.43)§</td>
<td>1.6 (0.8–3.2)</td>
</tr>
<tr>
<td>Pplat at admission,* cm H₂O</td>
<td>22 (6)</td>
<td>23 (7)</td>
<td>1.02 (0.96–1.1)</td>
<td></td>
</tr>
<tr>
<td>PEEP at admission,* cm H₂O</td>
<td>7 (3)</td>
<td>8 (4)</td>
<td>1.1 (0.97–1.3)</td>
<td></td>
</tr>
<tr>
<td>SOFA score∥</td>
<td>7 (2–18)</td>
<td>10 (3–21)</td>
<td>1.18 (1.08–1.29)¶</td>
<td>1.18 (1.07–1.3)¶</td>
</tr>
<tr>
<td>Δ SOFA score∥</td>
<td>0 (0–8)</td>
<td>0.5 (0–15)</td>
<td>1.21 (1.07–1.36)¶</td>
<td>1.24 (1.09–1.41)¶</td>
</tr>
</tbody>
</table>

- Chest 2006;130:724-729

groups (5 days [interquartile range (IQR), 6 days] vs 5 days [IQR, 9.5 days], respectively, in patients
with ALI/ARDSp and ALI/ARDSexp; p = 0.4). The hospital mortality rate was 47.8% and was not
significantly different between the two groups (ALI/ARDSp group, 43.1%; ALI/ARDSexp group,
57.9%; p = 0.06). Multivariate analysis showed the following risk factors for death in the ICU: female
sex, Pplat at admission, and ARDSexp patients.
Possible reasons

- LTV in clinical practice is yet to be accepted universally
- Mortality is affected predominantly by other components, especially sepsis and MODS
- Previous studies also used TV to the tune of 7-9ml/Kg and not 12 ml/Kg as was used in ‘Tidal volume trial’
To conclude

• LTV Ventilation has definite mortality benefit, both in short and long term and needs to be accepted and used routinely

• Our practice-
  – To start with 6 ml/Kg IBW and titrate according to SpO2 and Pplat at bedside
How do I know my patient will require more than usual?

1. P/F ratio <100
2. PEEP >15 – Attributable mortality 16%
3. Inability to maintain Pplat <30 cmH2O despite a Vt 4 mL/kg IBW
4. Oxygenation Index \([\text{FIO2} \times \text{mPaw} \times 100]/\text{PaO2}\)  > 30
5. Little improvement in P/F ratio after 24 hours of LPV – Mortality 53-68%
6. Development of barotrauma

-Esan A. et al. CHEST 2010; 137( 5 ): 1203 – 1216
• What next??
Wait - Is it really refractory hypoxemia?

• Check
  – Is the Vt appropriate?
  – Is there VP asynchrony?
  – Is there fluid overload/cardiogenic component?
  – Is there a device malfunction?
How do I go about refractory hypoxemia in severe ARDS?

Rescue therapy-

- ECMO
- Higher PEEP
- Recruitment maneuver
- HFOV/HFPV
- Prone positioning
- APRV
Unconventional strategies

Physiological Rationale-

- Recruit collapsed but potentially recruitable alveoli
- Optimize V/P matching
- Without further increasing lung injury

Rationalization from Clinical trials-

- 16% of early deaths in ARDS are due to refractory hypoxemia
- Most of the rescue therapies are proven to improve oxygenation

-Esan A. et al. CHEST 2010; 137( 5 ): 1203 – 1216
Recruitment Maneuver -

Rationale -
1. ARDS lung is derecruited and recruitable

2. Concept of COP of the lung units
   • COP varies from relatively low to very high

3. Lung recruitment is beneficial
   • increase in the aerated lung mass- minimize the lung heterogeneity and to increase the size of the baby lung
   • Prevention of atelectatotrauma

Recruitment cont..

It is a transient increase in transpulmonary pressure intended to promote reopening of collapsed alveoli- function of lung inflation
• Used to identify and utilize alveoli which are collapse but are potentially recruitable without further lung injury

• Useful only if patient is on modest PEEP

• Improvement in oxygenation- indicates PEEP being used was inadequate

• Should be followed by high PEEP to maintain benefits
Recruitment, Evidence:

- No properly conducted RCT
- Only Case series/ data from other ARDS studies
- No standard maneuver

-Esan A. et al. CHEST 2010; 137( 5 ): 1203 – 1216
Recruitment, evidence-

Duration of hold-

• Early ARDS - most of the recruitment occurs during the first 10 s of a SI RM

• Hemodynamic impairment is significant after the tenth second of RM

Recruitment Maneuvers for Acute Lung Injury
A Systematic Review

Eddy Fan¹,², M. Elizabeth Wilcox¹, Roy G. Brower², Thomas E. Stewart¹, Sangeeta Mehta¹, Stephen E. Lapinsky¹, Maureen O. Meade³, and Niall D. Ferguson¹

¹Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, Ontario, Canada; ²Division of Pulmonary and Critical Care Medicine, Johns Hopkins University, Baltimore, Maryland; and ³Departments of Clinical Epidemiology and Biostatistics, and Medicine, McMaster University, Hamilton, Ontario, Canada

Rationale: There are conflicting data regarding the safety and efficacy of recruitment maneuvers (RMs) in patients with acute lung injury (ALI).

Objectives: To summarize the physiologic effects and adverse events in adult patients with ALI receiving RMs.

Methods: Systematic review of case series, observational studies, and randomized clinical trials with pooling of study-level data.

Measurements and Main Results: Forty studies (1,185 patients) met inclusion criteria. Oxygenation (31 studies; 636 patients) was significantly increased after an RM (Pao₂: 106 versus 193 mm Hg, P = 0.001; and Pao₂/FiO₂ ratio: 139 versus 251 mm Hg, P < 0.001). There were no persistent, clinically significant changes in hemodynamic parameters after an RM. Ventilatory parameters (32 studies; 548 patients) were not significantly altered by an RM, except for higher PEEP post-RM (11 versus 16 cm H₂O; P = 0.02). Hypotension (12%) and desaturation (9%) were the most common adverse events (31 studies; 985 patients). Serious adverse events (e.g., barotrauma [1%] and arrhythmias [1%]) were infrequent. Only 10 (1%) patients had their RMs terminated prematurely due to adverse events.

What this Study Adds to the Field
Given the uncertain benefit of transient oxygenation improvements in patients with ALI and the lack of information on their influence on clinical outcomes, the routine use of RMs cannot be recommended or discouraged at this time. RMs should be considered for use on an individualized basis in patients with ALI who have life-threatening hypoxemia.
### Table 1: Summary of Results of Three Randomized Controlled Trials of Lower vs Higher Levels of PEEP

<table>
<thead>
<tr>
<th>Study</th>
<th>Control Group</th>
<th>Experimental Group</th>
<th>Major Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALVEOLI</td>
<td>Volume assist-control. VT = 6 mL/kg IBW. Pplat ≤ 30 cm H₂O. Combinations of PEEP and Fio₂ to maintain PaO₂ (55-80 mm Hg) or SpO₂ (88%-95%). PEEP on days 1-4 was 8.3 ± 3.2 cm</td>
<td>Volume assist-control. VT = 6 mL/kg IBW. Pplat ≤ 30 cm H₂O. Combinations of PEEP and Fio₂ to maintain PaO₂ (55-80 mm Hg) or SpO₂ (88%-95%). PEEP on days 1-4 was 13.2 ± 3.5 cm</td>
<td>Higher PaO₂/Fio₂ ratio in high PEEP group (220 ± 89 vs 168 ± 66) on day 1. Higher compliance in the higher-PEEP group (30 ± 34 vs 31 ± 15 mL/cm H₂O) on day 1. Mortality before hospital discharge (low PEEP, 24.9%; high PEEP, 27.5%; P = .48). Ventilator-free days (low PEEP, 14.5 ± 10.4 d; high PEEP, 13.8 ± 10.6 d; P = .50). Incidence of barotrauma (low PEEP, 10%; high PEEP, 11%; P = .51).</td>
</tr>
<tr>
<td>LOV</td>
<td>Volume assist-control. VT = 6 mL/kg IBW. Pplat ≤ 30 cm H₂O. Combinations of PEEP and Fio₂ to maintain PaO₂ (55-80 mm Hg) or SpO₂ (88%-93%). PEEP on days 1-3 was 9.8 ± 2.7 cm</td>
<td>Pressure control. VT = 6 mL/kg IBW. Pplat ≤ 40 cm H₂O. Combinations of PEEP and Fio₂ to maintain PaO₂ (55-80 mm Hg) or SpO₂ (85%-93%). PEEP on days 1-4 was 14.6 ± 3.4 cm</td>
<td>Recruitment maneuvers after each disconnect from the ventilator of 40 cm H₂O for 40 s. n = 475</td>
</tr>
<tr>
<td>EXPRESS</td>
<td>Volume assist-control. VT = 6 mL/kg IBW. Moderate PEEP (5-9 cm H₂O). n = 382</td>
<td>Volume assist-control. VT = 6 mL/kg IBW. PEEP set to reach Pplat of 28-30 cm H₂O (14.6 ± 3.2 cm H₂O) on day 1. n = 385</td>
<td>Higher PaO₂/Fio₂ ratio in higher-PEEP group (218 ± 97 vs 150 ± 69) on day 1. Higher compliance in the high-PEEP group (37.2 ± 22.7 mL/cm H₂O vs 33.7 ± 14.3 mL/cm H₂O) on day 1. The increased PEEP group had higher median number of ventilator-free days (7 d vs 3 d; P = .04), organ failure-free days (6 d vs 2 d; P = .04), and use of adjutantive therapies. Incidence of barotrauma (high PEEP, 11.2%; low PEEP, 9.1%; P = .33).</td>
</tr>
</tbody>
</table>

-Esan A. et al. CHEST 2010; 137(5): 1203 – 1216
However...

- Higher PEEP was safe
- Sub group analysis of refractory hypoxemia group
  - Lesser numbers requiring salvage therapy (10% vs. 20%)
  - Alveoli trial was not based on identification of LIP & PEEP was arbitrarily set as per table
- Definite role in subset of patients with severe lung injury

- Briel M et al. JAMA. 2010;303(9):865-873
- Esan A. et al. CHEST 2010; 137(5): 1203 – 1216
Which patient will benefit?

- 30 minute trial of high PEEP
- B/L lung involvement
- Recruitable lung

Optimal PEEP- No clear evidence-
- Incremental or decremental PEEP
- Esophageal pressure- unreliable
- PV tool- LIP useful
- Stress Index-

-Esan A. et al. CHEST 2010; 137( 5 ): 1203 – 1216
Stress index

-Esan A. et al. CHEST 2010; 137( 5 ): 1203 – 1216
Combining above three strategies (LOVS)

**Ventilation Strategy Using Low Tidal Volumes, Recruitment Maneuvers, and High Positive End-Expiratory Pressure for Acute Lung Injury and Acute Respiratory Distress Syndrome**

A Randomized Controlled Trial

**Results**  Eighty-five percent of the 983 study patients met criteria for acute respiratory distress syndrome at enrollment. Tidal volumes remained similar in the 2 groups, and mean positive end-expiratory pressures were 14.6 (SD, 3.4) cm H₂O in the experimental group vs 9.8 (SD, 2.7) cm H₂O among controls during the first 72 hours (P < .001). All-cause hospital mortality rates were 36.4% and 40.4%, respectively (relative risk [RR], 0.90; 95% confidence interval [CI], 0.77-1.05; P = .19). Barotrauma rates were 11.2% and 9.1% (RR, 1.21; 95% CI, 0.83-1.75; P = .33). The experimental group had lower rates of refractory hypoxemia (4.6% vs 10.2%; RR, 0.54; 95% CI, 0.34-0.86; P = .01), death with refractory hypoxemia (4.2% vs 8.9%; RR, 0.56; 95% CI, 0.34-0.93; P = .03), and previously defined eligible use of rescue therapies (5.1% vs 9.3%; RR, 0.61; 95% CI, 0.38-0.99; P = .045).

Meade MO et al. JAMA. 2008;299(6):637-645
PCIRV

Rationale
• Maintains recruitment
• More time for oxygenation
• Improves oxygenation

Problems
• Requires sedation and paralysis
• Uncomfortable
• Risk of Auto PEEP & haemodynamic compromise

• Evidence does not show any benefit over LPV

-Esan A. et al. CHEST 2010; 137( 5 ): 1203 – 1216
APRV

- Conceptually continuum of IRV
- Separates 2 Pumps
- Recruitment- Maximizes benefit of PPV & SV
- Allows asynchrony without adverse effects on oxygenation
- Improves patient comfort
- Allows OLV at relatively low pressure swings

-Esan A. et al. CHEST 2010; 137(5): 1203 – 1216
## APRV evidence

<table>
<thead>
<tr>
<th>Author, yr</th>
<th>No of pt.</th>
<th>Mortality</th>
<th>comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Putensen et al. 2001</td>
<td>30</td>
<td>20 vs 26%</td>
<td>Safe, Comfortable for patient</td>
</tr>
<tr>
<td>Verpula et al.</td>
<td>33</td>
<td>8 vs 14%</td>
<td>No mortality benefit over LPV, Not recommended routinely</td>
</tr>
<tr>
<td>Verpula et al.</td>
<td>58</td>
<td>17 vs 18%</td>
<td></td>
</tr>
</tbody>
</table>

-Esan A. et al. CHEST 2010; 137(5): 1203 – 1216
HFOV

Rationale-

- Maintain open lung
- Minimal volume swings

Achieved by-

- Higher mean pressure
- Frequency increased to minimize fall in airway pressure
- VT decreased to compensate for possible auto PEEP
- VT = dead space - oscillatory pattern
## HFOV: Evidence -

<table>
<thead>
<tr>
<th>Author, yr</th>
<th>No. of patients</th>
<th>Result</th>
<th>comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Derdak et al. 2002</td>
<td>148</td>
<td>- No survival benefit</td>
<td>Safe</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Improved oxygenation</td>
<td>Efficacy compared to LPV needs to be proven</td>
</tr>
<tr>
<td>Bollen et al. 2005</td>
<td>61 Stopped</td>
<td>No survival benefit</td>
<td>Can be used as salvage therapy</td>
</tr>
<tr>
<td></td>
<td>prematurely</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

When Caring for Critically Ill Patients, Do Clinicians Have a Responsibility to Be Innovative and Try Unproven Approaches When Accepted Approaches Are Failing?

Bruce K Rubin MEgr MD MBA FAARC and Kenneth P Steinberg MD

Table 1. Research Versus “Adventurism”

<table>
<thead>
<tr>
<th>Research</th>
<th>Adventurism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distinguishes helpful from unhelpful, or even harmful, therapies</td>
<td>Fails to advance knowledge</td>
</tr>
<tr>
<td>Vital to improving care</td>
<td>Unable to distinguish benefit from harm</td>
</tr>
<tr>
<td>Advances knowledge, even if it doesn’t help the individual patient</td>
<td>Often leads to false conclusions</td>
</tr>
<tr>
<td>Generates evidence</td>
<td>Ignores evidence</td>
</tr>
</tbody>
</table>
To conclude

• Use what is available

• Use the one which you are well versed with

• When faced with a patient with refractory hypoxemia-
  Rescue strategy of ventilation may be life saving in
  individual patient and is worth trying for….

• However if no benefit is observed over few hours of trial-
  it should abandoned
Non ventilatory strategies

Rapid Rescue from hypoxemia-
1. Neuromuscular blockade
2. Inhaled vasoactive agents
3. Prone positioning
4. Extracorporeal life support

Gradual rescue from hypoxemia-
1. Conservative fluid management
2. Intravenous corticosteroids
3. Nutritional modification

Neuromuscular blockade

3 RCTs- Latest ACURASyS trial
- Significant improvement in oxygenation
- Benefit seen despite absence of VP asynchrony at baseline
- Lower concentrations of proinflammatory cytokines
- Survival benefit at 90 days- ACURASyS study

Problem-
- Critical care myopathy esp. with concurrent steroids

Present status-
- Can be used if first dose shows significant improvement, No major adverse events

Inhaled NO

Rationale-

- Selective vasodilation- Improved V/Q matching
- lower PAP

Evidence- 5 RCTs, 1 systemic review, 1 metaanalysis-

- Transient improvement in oxygenation 24-96hrs
- No survival benefit or reduction in ventilator-free days

Inhaled NO

Problems-

• Cost
• Renal dysfunction
• Methemoglobinemia- rare at dose<80ppm

Present status-

• Can be used in refractory hypoxemia
• Discontinue if no benefit in 1 hour

Other vasoactive drugs

- IV Phenylephrine-
- Prostacyclins- Cheaper alternative to iNO
- Almitrine- Potentiates HPV
- Avoid systemic vasodilators
  - All conceptually sound
  - Improve oxygenation in short term

Prone position: Physiological Rationale-

• Recruitment

• Redistribution of ventilation -enhanced V/Q matching

• Elimination of compression of the lungs by the heart

• Decreased shunt

• Improved compliance

### Table 1—Summary of Four Randomized Trials on Prone Position

<table>
<thead>
<tr>
<th>Enrollment criteria</th>
<th>Gattinoni et al&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Guerin et al&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Mancebo et al&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Taccone et al&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>304</td>
<td>791</td>
<td>136</td>
<td>343</td>
</tr>
<tr>
<td>Prone</td>
<td>152</td>
<td>413</td>
<td>76</td>
<td>168</td>
</tr>
<tr>
<td>Supine</td>
<td>152</td>
<td>378</td>
<td>60</td>
<td>174</td>
</tr>
<tr>
<td>Daily proning</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Planned</td>
<td>&gt; 6 h/d</td>
<td>&gt; 8 h/d</td>
<td>20 h/d</td>
<td>20 h/d</td>
</tr>
<tr>
<td>Actual</td>
<td>7 h/d</td>
<td>8 h/d</td>
<td>13 h/d</td>
<td>18-20 h/d</td>
</tr>
<tr>
<td>Number of days</td>
<td>10 d</td>
<td>4 d</td>
<td>10 d</td>
<td>28 d</td>
</tr>
<tr>
<td>Oxygenation</td>
<td>Improved</td>
<td>Improved</td>
<td>Improved</td>
<td>Improved</td>
</tr>
<tr>
<td>VAP</td>
<td>Not assessed</td>
<td>Reduced</td>
<td>Not reduced</td>
<td>Not assessed</td>
</tr>
<tr>
<td>Primary end point</td>
<td>10-d mortality</td>
<td>28-d mortality</td>
<td>ICU mortality</td>
<td>28-d mortality</td>
</tr>
<tr>
<td></td>
<td>21.1% vs 25%</td>
<td>32.4% vs 31.5%</td>
<td>43% vs 58%</td>
<td>31.0% vs 32.8%</td>
</tr>
<tr>
<td>Relative risk (RR)</td>
<td>0.84</td>
<td>0.97</td>
<td>0.74</td>
<td>0.97</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.56-1.27</td>
<td>0.79-1.19</td>
<td>0.53-1.04</td>
<td>0.84-1.13</td>
</tr>
<tr>
<td><em>P</em></td>
<td>.50</td>
<td>.77</td>
<td>.12</td>
<td>.72</td>
</tr>
</tbody>
</table>

ALI = acute lung injury; RR = relative risk; VAP = ventilator-associated pneumonia.

Analyzing the latest trial- Prone-Supine II Study

- Only ARDS patients
- Stratification in moderate vs severe
- Prespecified ventilation protocol
- Early application <72 hrs
- Up to 20 hr/day

Results
- NO SURVIVAL BENEFIT
- More COMPLICATIONS
- Non significant trend towards survival benefit in severe group

Can be used in refractory patients with potential complications in mind

<table>
<thead>
<tr>
<th>Study</th>
<th>Prone, n/N</th>
<th>Supine, n/N</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short-term prone positioning</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leal et al&lt;sup&gt;22&lt;/sup&gt;</td>
<td>5/8</td>
<td>6/8</td>
<td>0.83 (0.43-1.63)</td>
</tr>
<tr>
<td>Papazian et al&lt;sup&gt;29&lt;/sup&gt;</td>
<td>3/13</td>
<td>5/13</td>
<td>0.60 (0.18-2.01)</td>
</tr>
<tr>
<td>Demory et al&lt;sup&gt;32&lt;/sup&gt;</td>
<td>4/13</td>
<td>6/15</td>
<td>0.77 (0.28-2.14)</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>34</td>
<td>36</td>
<td>0.77 (0.46-1.28)</td>
</tr>
<tr>
<td>Overall effect p = 0.32. Heterogeneity I^2 = 0%.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Prolonged prone positioning</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gattinoni et al&lt;sup&gt;23&lt;/sup&gt;</td>
<td>77/152</td>
<td>73/152</td>
<td>1.05 (0.84-1.32)</td>
</tr>
<tr>
<td>Beuret et al&lt;sup&gt;24&lt;/sup&gt;</td>
<td>3/12</td>
<td>4/9</td>
<td>0.56 (0.17-1.91)</td>
</tr>
<tr>
<td>Guerin et al&lt;sup&gt;27&lt;/sup&gt;</td>
<td>134/413</td>
<td>119/378</td>
<td>1.03 (0.84-1.26)</td>
</tr>
<tr>
<td>Curley et al&lt;sup&gt;28&lt;/sup&gt;</td>
<td>4/51</td>
<td>4/51</td>
<td>1.00 (0.26-3.78)</td>
</tr>
<tr>
<td>Voggenreiter et al&lt;sup&gt;30&lt;/sup&gt;</td>
<td>1/21</td>
<td>3/19</td>
<td>0.30 (0.03-2.66)</td>
</tr>
<tr>
<td>Mancebo et al&lt;sup&gt;31&lt;/sup&gt;</td>
<td>33/76</td>
<td>35/60</td>
<td>0.74 (0.53-1.04)</td>
</tr>
<tr>
<td>Chan et al&lt;sup&gt;34&lt;/sup&gt;</td>
<td>4/11</td>
<td>4/11</td>
<td>1.00 (0.33-3.02)</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>736</td>
<td>680</td>
<td>0.97 (0.85-1.11)</td>
</tr>
<tr>
<td>Overall effect p = 0.68. Heterogeneity I^2 = 0%.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>770</td>
<td>716</td>
<td>0.96 (0.84-1.09)</td>
</tr>
<tr>
<td>Overall effect p = 0.52. Heterogeneity I^2 = 0%.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ECMO in ARDS

3 RCTs in adults, total 330 patients

- First 2 trials, 110 patients- no mortality benefit
- CESAR trial- serious methodological flaws- significant mortality benefit- however conclusion is not possible
- Can be considered as rescue therapy in suitably selected patients

ECMO in ARDS

Indications (as a temporary rescue measure)
- Acute
- Life threatening
- Reversible
- Unresponsive to conventional therapy
- Ventilation <7 days
- Age <65 years
- PO2 / FiO2 < 60 (in spite of standard care)
- No significant comorbidities

Comparison of Two Fluid-Management Strategies in Acute Lung Injury

The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network

RESULTS
The rate of death at 60 days was 25.5 percent in the conservative-strategy group and 28.4 percent in the liberal-strategy group (P=0.30; 95 percent confidence interval for the difference, −2.6 to 8.4 percent). The mean (±SE) cumulative fluid balance during the first seven days was −136±491 ml in the conservative-strategy group and 6992±502 ml in the liberal-strategy group (P<0.001). As compared with the liberal strategy, the conservative strategy improved the oxygenation index ([mean airway pressure × the ratio of the fraction of inspired oxygen to the partial pressure of arterial oxygen] × 100) and the lung injury score and increased the number of ventilator-free days (14.6±0.5 vs. 12.1±0.5, P<0.001) and days not spent in the intensive care unit (13.4±0.4 vs. 11.2±0.4, P<0.001) during the first 28 days but did not increase the incidence or prevalence of shock during the study or the use of dialysis during the first 60 days (10 percent vs. 14 percent, P = 0.06).

CONCLUSIONS
Although there was no significant difference in the primary outcome of 60-day mortality, the conservative strategy of fluid management improved lung function and shortened the duration of mechanical ventilation and intensive care without increasing nonpulmonary-organ failures. These results support the use of a conservative strategy of fluid management in patients with acute lung injury. (ClinicalTrials.gov number, NCT00281268.)
But—

- Martin et al. failed to show significant difference in placebo and diuretics + albumin
- In another study they reported beneficial role of Albumin + Furosemide over furosemide alone especially in patients with hypoproteinemia
  

- So what do we take from it?
- Difficult to say at present- till it is solved...

---

Table 2—Simplified Algorithm for Conservative Management of Fluids in Patients With ALI, Based on Protocol Used in the FACIT³

<table>
<thead>
<tr>
<th>CVP, mm Hg (Recommended)</th>
<th>PAOP, mm Hg (Optional)</th>
<th>MAP ≥ 60 mm Hg and Not Receiving Vasopressors for ≥ 12 h</th>
<th>Average Urine Output &lt; 0.5 mL/kg/h</th>
<th>Average Urine Output ≥ 0.5 mL/kg/h</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 8</td>
<td>&gt; 12</td>
<td>Furosemide†; reassess in 1 h</td>
<td>Furosemide; reassess in 4 h</td>
<td></td>
</tr>
<tr>
<td>4-8</td>
<td>8–12</td>
<td><strong>Fluid bolus as fast as possible†; reassess in 1 h</strong></td>
<td>Furosemide; reassess in 4 h</td>
<td></td>
</tr>
<tr>
<td>≤ 4</td>
<td>&lt; 8</td>
<td><strong>Fluid bolus as fast as possible†; reassess in 1 h</strong></td>
<td>No intervention; reassess in 4 h</td>
<td></td>
</tr>
</tbody>
</table>

*(CHEST 2007; 131:913–920)*
Steroids

- Early
  - Improved oxygenation
  - More ventilator free & shock free days

Metaanalysis by Tang BM et al.

- Lower overall relative risk for death, ICU LOS, and multiple organ dysfunction scale score
- No increase in infection, neuromyopathy, or major complications with corticosteroids.

- Meduri GU et al. JAMA. 1998;280(2):159-165
<table>
<thead>
<tr>
<th>Time</th>
<th>Administration form</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early severe ARDS ((\text{PACO}_2: \text{FiO}_2 &lt; 200) on positive end-expiratory pressure 10 cm H(_2)O)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loading</td>
<td>Bolus over 30 min</td>
<td>1 mg/kg</td>
</tr>
<tr>
<td>Days 1–14(\text{abc})</td>
<td>Infusion at 10 mL/h</td>
<td>1 mg/kg/d</td>
</tr>
<tr>
<td>Days 15–21(\text{ac})</td>
<td>Infusion at 10 mL/h</td>
<td>0.5 mg/kg/d</td>
</tr>
<tr>
<td>Days 22–25(\text{ac})</td>
<td>Infusion at 10 mL/h</td>
<td>0.25 mg/kg/d</td>
</tr>
<tr>
<td>Days 26–28(\text{ac})</td>
<td>Infusion at 10 mL/h</td>
<td>0.125 mg/kg/d</td>
</tr>
<tr>
<td>Unresolving ARDS (less than one-point reduction in lung injury score by day 7 of ARDS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loading</td>
<td>Bolus over 30 min</td>
<td>2 mg/kg</td>
</tr>
<tr>
<td>Days 1–14(\text{abc})</td>
<td>Infusion at 10 mL/h</td>
<td>2 mg/kg/d</td>
</tr>
<tr>
<td>Days 15–21(\text{ac})</td>
<td>Infusion at 10 mL/h</td>
<td>1 mg/kg/d</td>
</tr>
<tr>
<td>Days 22–25(\text{ac})</td>
<td>Infusion at 10 mL/h</td>
<td>0.5 mg/kg/d</td>
</tr>
<tr>
<td>Days 26–28(\text{ac})</td>
<td>Infusion at 10 mL/h</td>
<td>0.25 mg/kg/d</td>
</tr>
<tr>
<td>Days 29–30(\text{ac})</td>
<td>Bolus over 30 min</td>
<td>0.125 mg/kg/d</td>
</tr>
</tbody>
</table>