Pulmonary & Extra-pulmonary ARDS: FIZZ or FUSS?

Dr. Rajagopala Srinivas
Senior Resident,
Dept. Pulmonary Medicine,
PGIMER, Chandigarh.
"The etiology of this respiratory distress syndrome remains obscure. Despite a variety of physical and possibly biochemical insults, the response of the lung was similar in all 12 patients. In view of the similar response of the lung to a variety of stimuli, a common mechanism of injury may be postulated"

The AECC (American European conference) later defined two subsets in their consensus conference:

“a direct ("primary" or "pulmonary") insult, that directly affects lung parenchyma, and an indirect ("secondary" or "extra-pulmonary") insult, that results from an acute systemic inflammatory response”

Bernard GR, Artigas A, Brigham KL, et al
Useful concept or distinctive sub-groups?

Acute Respiratory Distress Syndrome Caused by Pulmonary and Extrapulmonary Disease
Different Syndromes?

LUCIANO GATTINONI, PAOLO PELOSI, PETER M. SUTER, ALESSIA PEDOTO, PAOLA VERCESI, and ALFREDO LISSONI

Istituto di Anestesia e Rianimazione, Universita’ di Milano and Servizio di Anestesia e Rianimazione, Ospedale Maggiore IRCCS, Milano, Italy; and Division of Surgical Intensive Care, University Hospital of Geneva, Geneva, Switzerland

12 patients with ARDSp and 9 patients of ARDSexp

Est (L) more in ARDSp and Est (w) more in ARDSexp

IAP more in ARDSexp and co-related with Est

Increase in PEEP lead to rise of Est in ARDSp and fall of Est in ARDSexp (more recruitment in ARDSexp)

Different respiratory mechanics and response to PEEP observed consistent with a prevalence of consolidation in ARDSp Vs prevalent edema and alveolar collapse in ARDSexp

# Lump or split?

**SPLIT?**
- Etiological events are distinct
- Pathogenetically different
- Morphology differs
- Physiologically distinguishable
- Varied responses to Rx
  - PEEP
  - Prone pressure ventilation
- Response to inhaled vasodilators different

**Lump?**
- Etiological case mix common
- Practical difficulties in case assignment
- Current clinical management similar
- Not related to outcomes
Are ARDSp and ARDSexp different?

1) Epidemiology
2) Pathophysiology
3) Morphological aspects
4) Respiratory mechanics
5) Ventilatory strategies
6) Response to pharmacological agents and
7) Long-term recovery
1. Epidemiology: Is ARDSp more common than ARDSexp?

In most studies, ARDSp more common than ARDSexp

Varies from 47-75% of total

*Study from our centre*

N=180

ARDSp (pneumonia most common)=123

ARDSexp (sepsis most common)=57

In the largest study (n=902), the incidence of both were equal
Why the discrepancy?

The lack of agreement among various studies because

1. Baseline status differ
2. Prevalence of the disease precipitating ARDS in each center
3. Impact of therapy and
4. Overall distribution of these factors in the studied population.
Early Direct injury
Pulmonary contusion
Inhalational injuries
Aspiration
Near-drowning
Fat emboli

Models (tracheal instillation of endotoxin, complement, TNF∞ or bacteria)

Damage to alveolar epithelium

Localization early to intra-alveolar space

Alveolar filling by edema, fibrin, collagen, neutrophilic aggregates, and/or blood

Pulmonary consolidation
Early ARDS exp
Sepsis
Pancreatitis
Massive transfusion
Drug overdosage

Models (intravenous or intraperitoneal toxic injection)

Damage to endothelium

Localization early to interstitium

Increase of vascular permeability and recruitment of monocytes, PMN’S, platelets

Primarily microvascular congestion and interstitial edema
1. In late stages, however it is homogenous.
2. Both might be simultaneously operative.
### 3. Morphology

#### Alveoli

<table>
<thead>
<tr>
<th></th>
<th>ARDSp</th>
<th>ARDSexp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alveolar epithelium</td>
<td>++Damage</td>
<td>Damage</td>
</tr>
<tr>
<td>Altered type I and II cell</td>
<td>++Damage</td>
<td>Normal</td>
</tr>
<tr>
<td>Alveolar neutrophils</td>
<td>Prevalent</td>
<td>Rare</td>
</tr>
<tr>
<td>Apoptotic neutrophils</td>
<td>Prevalent</td>
<td>Rare</td>
</tr>
<tr>
<td>Fibrinous exudates</td>
<td>Present</td>
<td>Rare</td>
</tr>
<tr>
<td>Alveolar collapse</td>
<td>++Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Local interleukin</td>
<td>Prevalent</td>
<td>Rare</td>
</tr>
</tbody>
</table>

#### Interstitial space

<table>
<thead>
<tr>
<th></th>
<th>ARDSp</th>
<th>ARDSexp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interstitial oedema</td>
<td>Absent</td>
<td>High</td>
</tr>
<tr>
<td>Collagen fibres</td>
<td>++Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Elastic fibres</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

#### Capillary endothelium

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>ARDSexp</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>++Damage</td>
</tr>
</tbody>
</table>

#### Blood

<table>
<thead>
<tr>
<th></th>
<th>ARDSp</th>
<th>ARDSexp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interleukin</td>
<td>Increased</td>
<td>++Increased</td>
</tr>
<tr>
<td>TNF-(\infty)</td>
<td>Increased</td>
<td>++Increased</td>
</tr>
</tbody>
</table>
Are ARDSp and ARDSexp morphologically distinct?

Cannot be reliably distinguished from each other

Predominance of alveolar collapse, fibrinous exudate and alveolar wall oedema in ARDSp

Collagen content in ARDSp > ARDSexp in the early phase, while no differences in elastin content.


4. Radiology: ARDSp vs. ARDSexp

Initial CT evaluation from Gattinoni’s group

N=33, ARDSp (22) and ARDSexp (11)

Consolidation and GGO equally present in ARDSp; asymmetric consolidation characteristic.

Predominant GGO in ARDSexp; more symmetric.

Pleural effusions in half; Kerley B and pneumatoceles uncommon.

One other evaluated this as a primary goal

N=41; ARDSp (16) and ARDSexp (25)

Significantly higher incidence of intense parenchymal opacification demonstrated in nondependent areas with direct insults

Inversely related to the time from intubation to CT

No single feature is predictive of either.

What can we conclude?

1. Increase in the lung densities most prominent in dependent lung regions in supine position

2) ARDSp due to CAP two prevalent patterns described:
   - Dependent extensive consolidation and air bronchograms with GGO
   - Homogeneous diffuse interstitial and alveolar infiltration, without evidence of atelectasis

3) In ARDSp, due to VAP, densities in the dependent part of the lung (likely atelectasis) are prevalent with the remaining nondependent lung substantially normal

4) ARDSexp has predominant GGO
5. Respiratory mechanics: ARDSp vs. ARDSexp

Seminal observations included “a stiff respiratory system” or loss of compliance.

Traditionally, this was assumed to be due to altered lung compliance.

When the abnormal compliance was partitioned,

- ARDSp-high lung elastance → consolidated lung
- ARDSexp- chest wall elastance → raised intra-abdominal pressure and gut edema.

Respiratory system resistance is similar in ARDSp and ARDSexp.

However, chest wall resistance is greater in ARDSexp.

*So, at a given airway pressure, higher trans-pulmonary pressures are seen in ARDSp.*

So, what is the significance of this divergent respiratory mechanics?
ARDSp

Raised Est (RS)

Raised Est (L)  Normal/ low Est (W)

Elevated trans-pulmonary Pressure; low pleural pressures

Mechanical ventilation

Risk of barotrauma
ARDSexp

- Raised Est (RS)
- Normal/low Est (L)
- Raised Est (W)

- Normal trans-pulmonary Pressure; high pleural pressures

- Mechanical ventilation

- Risk of hemodynamic compromise
Ventilatory strategies: ARDSp vs. ARDSexp

1. Efficacy of low tidal volume ventilation

Efficacy of Low Tidal Volume Ventilation in Patients with Different Clinical Risk Factors for Acute Lung Injury and the Acute Respiratory Distress Syndrome

MARK D. EISNER, TAYLOR THOMPSON, LEONARD D. HUDSON, JOHN M. LUCE, DOUGLAS HAYDEN, DAVID SCHOENFELD, MICHAEL A. MATTHAY, and the Acute Respiratory Distress Syndrome Network

Division of Pulmonary and Critical Care Medicine, and Division of Occupational and Environmental Medicine, Department of Medicine, University of California, San Francisco; Pulmonary and Critical Care Medicine, and ARDS Network Clinical Coordinating Center, Massachusetts General Hospital, Harvard University; Pulmonary and Critical Care Medicine, Harborview Medical Center, University of Washington; Department of Biostatistics, Harvard School of Public Health; Department of Anesthesia and Cardiovascular Research Institute, University of California, San Francisco


Retrospective analysis of 902 patients; NO difference in efficacy.
6. Ventilatory strategies: ARDSp vs. ARDSexp

1. Application of PEEP.

Potential for recruitment more in atelectasis than in consolidation

Applied airway pressure may partition differently, leading to varying recruitment

Use of higher PEEP and higher Pi (Cstat_{res}) may be safer in ARDSexp since Cstat_{W} > Cstat_{L}

Time course to oxygenation may be different in ARDSp
ARDSp

Predominant consolidation
More alveolar flooding
Normal areas less

Application of PEEP

No/ minimal effect on abnormal areas

Alveolar over-distension in normal areas

Fall of Est (L)

Minimal improvement / Worsening hypoxemia
ARDS exp

Predominant collapse
less alveolar flooding
Normal areas more

Application of PEEP

Recruitment of collapse areas

Alveolar over-distension in
normal area ±

Rise of Est (L)

Hypoxemia improves
Does this translate into management differences?

In clinical practice, PEEP useful in ARDS irrespective of etiology
Clinically, it is possible that both ARDSP and ARDSEX have a mix of consolidation and collapse
Preponderance of one does not negate benefit of PEEP in ARDSP.
Other mechanisms of benefit might have a role
  Regional diversion of ventilation
  Regional diversion of perfusion
ARDS Net strategy did not use different strategy for both subgroups.

Low tidal ventilation efficacy same in both groups

*Am J Respir Crit Care Med Vol 164. pp 231–236, 2001*

Potentially,

1. Levels of PEEP can higher in ARDSexp (chest wall partitioning) before compliance falls

2. Volutrauma with higher PEEP less likely with ARDSexp
Ventilatory strategies: ARDSp vs. ARDSexp

1. Prone position ventilation

Mechanisms by which prone position acts:

1. Increase in FRC
2. Changes in diaphragm position/ movement
3. Secretions drainage
4. Gravity directed blood flow to less injured areas
5. Reduction of heart/ mediastinum compression
6. Changes in chest wall compliance

Raised intra abdominal pressure

Collapse vs consolidation
7. Whither data….?

2-hour physiological study (n=47); 31 ARDSp and 16 ARDSexp

In prone position
(1) the response in oxygenation more marked in ARDSexp compared with ARDSp (3 FOLD)
(2) Rate of increase in oxygenation slower in ARDSp
(3) the densities, determined that in prone position decreased to a greater degree in ARDSexp

Large prospective trial in 73 patients
51 ARDSp and 22 ARDSexp
Prone position for 6 h for 10 days
The improvement in oxygenation was greater in ARDSexp compared with ARDSp
Mortality was not different between the two groups

Response to pharmacological agents

Data on iNO and prostacyclin are non-conclusive
Response to iNO greater in ARDSp
Attributed to greater shunting


However, response to prostacyclin greater in ARDSexp

Are long term outcomes different in ARDSp and ARDSexp?

Influence of direct and indirect etiology on acute outcome and 6-month functional recovery in acute respiratory distress syndrome

Ganesh Suntharalingam, FRCA; Kate Regan, MRCP; Brian F. Keogh, FRCA; Clifford J. Morgan, FRCA; Timothy W. Evans, MD, PhD

Crit Care Med 2001; 29: 562-7

No difference in FVC and DLco between the two groups
8. Mortality: ARDSp vs. ARDSexp

Also non-pulmonary organ failure and time to liberation from mechanical ventilation similar.
I have been doomed to such a dreadful shipwreck that man is not truly one, but truly two. I say two, because the state of my own knowledge does not pass beyond that point. Others will follow, others will outstrip me on the same lines; and I hazard the guess that man will be ultimately known for a mere polity of multifarious, incongruous, and independent denizens.
Two-face or multi-faced??

<table>
<thead>
<tr>
<th>Clinical Risk Factor</th>
<th>Low Vt Ventilation* (n = 473)</th>
<th>Traditional Vt Ventilation (n = 429)</th>
<th>All Patients† (n = 902)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis</td>
<td>38% (47/125)</td>
<td>50% (55/111)</td>
<td>43% (102/236)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>31% (50/162)</td>
<td>42% (66/158)</td>
<td>36% (116/320)</td>
</tr>
<tr>
<td>Aspiration</td>
<td>36% (26/72)</td>
<td>37% (23/62)</td>
<td>37% (49/134)</td>
</tr>
<tr>
<td>Trauma</td>
<td>12% (7/59)</td>
<td>11% (4/37)</td>
<td>11% (11/98)</td>
</tr>
<tr>
<td>Other</td>
<td>29% (16/55)</td>
<td>40% (25/61)</td>
<td>35% (41/116)</td>
</tr>
<tr>
<td>Total‡</td>
<td>31% (146/473)</td>
<td>40% (173/429)</td>
<td>35% (319/902)</td>
</tr>
</tbody>
</table>

*Vt = tidal volume
†Sepsis, pneumonia, aspiration, trauma, other
‡Total includes all patients

Summary

1. Prevalent damage in early stages of a direct insult is intra-alveolar whereas in indirect injury is interstitial edema.

2. Radiological pattern in ARDSp is prominent consolidation and ARDSexp is GGO.

3. Primary abnormalities are raised lung and chest wall elastance in ARDSp and ARDSexp respectively.

4. PEEP, inspiratory recruitment and prone position more effective in ARDSexp.

5. Further studies are warranted to better define if the distinction between ARDS of different origins can improve clinical management and survival.