ARDS Pathophysiology: Why does it make the Lung so Susceptible to VILI?

Gary F. Nieman
Associate Professor
Department of Surgery
Director, Critical Care Laboratory
Upstate Medical University
Syracuse, NY
Niemang@upstate.edu

Nieman Disclosures
- Consultant for Interxon Corporation
- NIH R01 grant: Development of a gene therapy approach to treat acute lung injury using a preclinical, large animal model
- Travel funded by Dräger Medical
- CUBR INO grant: A novel pleiotropic anti-inflammatory drug (TRB-N0224) to reduce ARDS incidence
- Equipment (ventilators, EIT, neonatal incubators) donated to Upstate Medical University by Dräger Medical
- Established an APRV Network website
- Conducted an APRV Workshop
- Patent for: “Method of preventing acute lung injury”
- Patent for: “Minimally invasive suction and treatment device (MIST)”
- Patent for: “Apparatus, system and method of assessing alveolar inflation”

“Physiology is the basis of medical reasoning, not statistics. Statistics are a tool”
Luciano Gattinoni
What are the Goals for Today?

• Review the science
  – What is the key pathophysiology of ARDS
  – What is the key pathophysiology of VILI

• With these pathological mechanisms in mind:

• What are the parameters that comprise a mechanical breath that can block these pathologic mechanisms?
The Impact of the Mechanical Breath on Micro-vascular Permeability and Fluid Flux

High Peak Pressures cause Stretch Induced Activation of TRPV4 Channels

\[ J_v = L_g S \left( \frac{P_c - P_i}{e^{-c \cdot t}} \right) \]

Pathologic Tetrad of ARDS

- Increased Capillary Permeability
- Alveolar Edema
- Alveolar Instability
- Surfactant Deactivation
Increased Interstitial Pressure

\[ J_v = L_p S [(P_c - P_i) - (\kappa - \nu)] \]


Pathologic Tetrad of ARDS

- Increased Capillary Permeability
- Alveolar Instability
- Surfactant Deactivation
- Alveolar Edema

Increased Airway Pressure

Increased Alveolar Space

Increased Interstitial Space

Increased Permeability

Increased Edema

Increased Volume
Pulmonary Perspective

The Role of Ventilation-induced Surfactant Dysfunction and Atelectasis in Causing Acute Respiratory Distress Syndrome

Richard K. Albert
Department of Medicine, Denver Health, Denver, Colorado, and University of Colorado, Arvada, Colorado

ARDS Pathogenesis: A tale of two cities.

Risk Factor → Inflammatory response

1. Mechanical Injury
2. Inflammatory response
3. Ards
4. Alveolar fluid
5. Surfactant dysfunction
6. Mechanical ventilation

Alpert R. AJRCCM 2012

The Impact of the Mechanical Breath on Pulmonary Surfactant

Risk of Ventilation-induced Surfactant Dysfunction and Atelectasis in Causing Acute Respiratory Distress Syndrome

Richard K. Albert
Department of Medicine, Denver Health, Denver, Colorado, and University of Colorado, Arvada, Colorado

ARDS Pathogenesis: A tale of two cities.

Risk Factor → Inflammatory response

1. Mechanical Injury
2. Inflammatory response
3. Ards
4. Alveolar fluid
5. Surfactant dysfunction
6. Mechanical ventilation

Alpert R. AJRCCM 2012
ARDS Pathogenesis: A tale of two cities.

Hypothesis

- Mechanical ventilation causes alterations to surfactant function before clinical symptoms.

Conclusions

Alteration of surfactant function are the consequence of the ventilator strategy.

Surfactant deactivation is a key mechanism of VILI.
Surfactant Stabilizes Alveoli

Pathologic Tetrad of ARDS

The Impact of the Mechanical Breath on Alveolar Mechanics

- Increased Capillary Permeability
- Alveolar Edema
- Alveolar Instability
- Surfactant Deactivation

Surfactant Stabilizes Alveoli

The Impact of the Mechanical Breath on Alveolar Mechanics

Surfactant Stabilizes Alveoli

The Impact of the Mechanical Breath on Alveolar Mechanics
In vivo Alveolar Mechanic Studies from our Lab

Schiller et al Crit Care Med 2001

In vivo Alveolar Mechanics

Normal

Acute Lung Injury
Protocol: ARDS (Tween) | Unstable Alveoli

1. Group 1: Stable Alveoli (Low Vt+High PEEP- Homogeneous)
2. Group 2: Unstable Alveoli (High Vt+Low PEEP- Heterogeneous)
Conclusion

Properly adjusted Mechanical Ventilation can reduce the severity of all components that comprise the Pathologic Tetrad of ARDS
What are the Goals for Today?
• Review the science
  – What is the key pathophysiology of ARDS
  – What is the key pathophysiology of VILI
• With these pathological mechanisms in mind:
• What are the parameters that comprise a mechanical breath that can block these pathologic mechanisms?

Why does the ARDS Tetrad Render the Lung so Vulnerable to VILI?

If Mechanical Stress Causes Excessive Strain Stress Failure & Severe Injury

Homogeneous Ventilation

Heterogeneous Ventilation

Roy S et al *Shock* 2013;39:28
What is the Mechanism of VILI at the Alveolar Level?

• Stress-concentrator
  – Open alveoli adjacent to collapsed or edematous alveoli

• Dynamic Strain
  – Collapsing and reopening of alveoli with each breath

Stress-concentrators occur between open alveoli and alveoli that are either collapsed or edema filled.
Inspiration: In Vivo Subpleural Alveoli

Expiration: In Vivo Subpleural Alveoli

Stress Concentration
What is the Mechanism of VILI at the Alveolar Level?

- Stress-concentrator
  - Open alveoli adjacent to collapsed or edematous alveoli

- Dynamic Strain
  - Collapsing and reopening of alveoli with each breath

Dynamic strain occurs when alveoli or alveolar ducts change size greatly with each tidal breath.
Dynamic Strain is Minimized by Increasing PEEP

What are the Goals for Today?

Tidal Volume

Does size matter?

With these pathological mechanisms in mind:

• What are the parameters that comprise a mechanical breath that can block these pathologic mechanisms?

Tidal Volume

Does size matter?
Micro-Anatomical Environment

• Tracheal Tidal Volume (t\(V_t\))
  - \(V_t\) delivered by the ventilator to the trachea

• Alveolar Tidal Volume (a\(V_t\))
  - The portion of \(V_t\) delivered to each individual alveoli

• The critical component that causes VILI is not the size of \(tV_t\), but the size of the a\(V_t\).

It is not just the absolute size of the tidal volume but rather the size of the tidal volume in relation to volume of the lung being ventilated

Lung Volume Change: CMV vs APRV

CMV: Vt 6cc/kg 
APRV: Vt 11cc/kg
Ventilation Near TLC

Each Alveolus as to change volume 25%

Inspiration

Expiration

Ventilation Near FRC

Two Alveoli change volume 66% and the other changes 100%

Inspiration

Expiration

Micro-Anatomical Environment
Change in Alveolar Size with Decreasing Number of Alveoli

Number of Alveoli (millions)

Change in Alveolar Size (um)

Vt = 500ml

Mechanical Breathing Profile of Airway Pressure
Release Ventilation
The Effect on Alveolar Recruitment and Microstrain in Acute Lung Injury

Michaela Kolrusch-Singule, MD; Bryanna Emr, O; Bradford Smith, PhD; Shreyas Roy, D; SUmeet Jain, D; Joshua Satalin, BS; Kathy Snyder; Penny Andrews, Rader Habash, D; Jason Bates, PhD, William Marx, DO; Gary·ernan, BA; Louis A. Gatt, PhD
It is not just the absolute size of the tidal volume but rather the size of the tidal volume in relation to volume of the lung being ventilated.

Gross Lung

High Resting Lung Volume (FRC) Minimizes VILI

- Reduces stress-concentrators
- Reduces dynamic strain
- Improves gas exchange
- Reduces Driving Pressure even with relatively large tidal volume
Driving Pressure

\[ \#P = \frac{V_t}{C_{RS}} \]
Tidal Volume, Driving Pressure and Lung injury in our Study

End of Experiment Ventilator Settings

<table>
<thead>
<tr>
<th></th>
<th>ARDSnet n=4</th>
<th>APRV n=4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tidal Volume/kg</td>
<td>5.77 ± 0.38</td>
<td>11.98 ± 0.77</td>
</tr>
<tr>
<td>PEEP</td>
<td>20 ± 2.31</td>
<td></td>
</tr>
<tr>
<td>FiO2</td>
<td>0.73 ± 0.15</td>
<td></td>
</tr>
<tr>
<td>Phigh</td>
<td></td>
<td>31.00 ± 3.51</td>
</tr>
<tr>
<td>Plow</td>
<td></td>
<td>0.0 ± 0.0</td>
</tr>
<tr>
<td>FIG2</td>
<td>8.21 ± 0.9</td>
<td></td>
</tr>
</tbody>
</table>

Gross Lung

ARDSnet

Vt = 6cc/kg

APRV

Vt = 12cc/kg

Roy et al. Shock 2013;39:28
What is happening in the microenvironment when tidal volume is high but driving pressure is low?
Micro-Anatomical Environment

- Tracheal Tidal Volume ($tV_t$)
  - $V_t$ delivered by the ventilator to the trachea

- Alveolar Tidal Volume ($aV_t$)
  - The portion of $tV_t$ delivered to each individual alveoli

- The critical component that causes VILI is not the size of $tV_t$, but the size of $aV_t$

When should we apply protective mechanical ventilation?

“Open the Lung and Keep the Lung Open”
B. Lachmann
*Intensive Care Med 1992*

“Never Let the Lung Collapse”
G.F. Nieman
*J Appl Physiol 2017*
Reducing ARDS Incidence during Major Surgery
Why is it Important to Prevent ARDS?

• Once established ARDS is very difficult to treat
  – Almost all clinical trials a failure (MacIntyre & Brower)
  – Low Vt only reduced ARDS moderately (ARDSnet)
  – Mortality of ARDS still 30-60% (Shari & Herridge)
  – Mortality is higher than Breast Cancer (Rubenfeld)
  – Even with Low Vt mortality still >40% (ALIEN study)

• Patients that develop established-ARDS often develop chronic lung and brain injury

Established-ARDS: Difficult to Treat

Mortality for Established ARDS

37.3%
Conclusion

Once Established it is very difficult to reduce ARDS mortality below 40%

Solution

Prevent ARDS before it develops in patients at high-risk

Is acute respiratory distress syndrome an iatrogenic disease?

- "...should we begin to consider that ALI/ARDS is a consequence of our efforts rather than progression of the underlying disease?"
- "...injurious ventilation strategies have been shown to cause all of the pathology associated with ALI/ARDS."
- "...ALI/ARDS is largely a 'man-made' syndrome."
- "...ALI/ARDS is no longer a syndrome that must be treated, but is a syndrome that should be prevented."
Summary

- Pathologic Tetrad
  - Increased vascular permeability
  - Alveolar edema
  - Surfactant deactivation
  - Alveolar instability
- VILI Mechanism
  - Stress-Risers
  - Alveolar collapse and reopening
- Low Tidal Volume
  - Not the size of the set Vt but the size of the alveolar Vt (AVt)
- ARDS Progressive Disease
  - Protect the lung as soon as the patient is intubated

In the Next Lecture

- Review the dynamic physiology of alveolar inflation and deflation
- Discuss how this dynamic physiology changes in acute lung injury (ALI) and what role this change plays as a VILI mechanisms
- Determine the optimal components of the mechanical breath that will normalize the change in dynamic alveolar mechanics during ALI
ARDS Pathophysiology: Why does it make the Lung so Susceptible to VILI?

7th Biennial Midwest Mechanical Ventilation and Critical Care Conference
September 29-30, 2017

Gary F. Nieman
Associate Professor
Department of Surgery
Director
Critical Care Laboratory
Upstate Medical University
Syracuse, NY
Nieman@upstate.edu

9/6/2017