VILI Mechanisms: Are Lung Regions Different?

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ISD Disclosures

Grant support to Denver Health Medical Center

- Dept. of Defense (CDMRP) Award 2012-2015 (PI)
  - Accelerate Diagnostics (development partner)
- NIH-NIAID R01 2015-2020
- U. Colorado AEF
- No Tobacco industry funding
- Accelerate Diagnostics, Cheetah Medical Ad Boards payment to DHMC
Lung Regional Differences:

- Lung regional manifestations of ARDS and VILI
- Lung regional embryogenesis
- What does prone position ventilation teach us about lung regional differences
- What are the future challenges for optimizing lung regional lung protection in ARDS
Severe ARDS: Dorso-basal predominant

Lung Inhomogeneities in ARDS

**Inhomogeneity:**
- Fraction of lung with inflation ratio > 95th % of control Increases with severity of ARDS
- Correlates with the $V_D/V_T$
- PEEP 45 cm H$_2$O ↓ inhomogeneities (18→12%)
- ↑ in nonsurvivors (20 vs. 17%)
- Independently associated with mortality

M. Cressoni, 2014 Am J Respir Crit Care Med 189, 149-158.
Regional Lung Derecruitment, Inflammation -16h MV Supine Sheep (Vt 8ml/kg, PEEP 0)

Regional net $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG) uptake

The Limits of Pathogenic Reduction

- Endothelial injury - ↑microvascular permeability – proteinacious edema
- PMN activation, degranulation
- Platelet activation
- Epithelial injury, apoptosis & denudation

M. Matthay, R. Zemans; Ann Rev Path. 2011; A Slutsky, V Ranieri . NEJM 2013;
Ventilator-Induced Lung Injury (VILI)

- Alveolar stress: Ratio of alveolar wall tension to thickness
- Lung strain: distending force - induced lung parenchymal deformation
- Cyclic distal airway open-close shearing
- Prevention
  - Low tidal volume (stretch)
  - PEEP/ recruitment
  - Permissive Hypercapnea
  - Prone positioning

Eur Respir J 2005 25:534-44
Uneven Distribution of Stress and Strain in the Injured Lung

- Regional inhomogeneity = “stress raiser”
- $P_{tp}$ safe in a homogeneous lung but locally harmful in the injured lung
- Ratio between the volume of two neighboring regions
  - Totally expanded : totally collapsed = 10:1 (30 cm H$_2$O)
  - Local pressure (stress): $30 \times (V_1/V_0)^{2/3} = 30 \times (10/1)^{2/3} = \sim 140$ cm H$_2$O

Lung regional metabolism is independent of cyclic recruitment/derecruitment

- Metabolic activity in tidal recruitment/derecruitment regions same as regions collapsed throughout the respiratory cycle;
- Metabolic activity of normally aerated tissue associated with
  - $P_{plat}$, (esp if $> 27 \text{ cm H}_2\text{O}$)
  - regional $V_t$ normalized by EELV.

G. Bellani AJRCCM 2011, 183, 1193-1199.
60-Day Survival Unassisted Breathing Adversely Affected by n-3 “Omega” FA or Albuterol

N-3 Omega Fatty Acid supplementation

- n-3 Supplement
  - Alive
  - Breathing without assistance
- Control
  - Alive
  - Breathing without assistance

Nebulized Albuterol

Rice, T. W. et al. JAMA 2011;306:1574-1581

Matthay MA, ..Douglas IS et.al; AJRCCM. 2011; 184(5):561-8
Lung Regional Differences:

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Murine Lung Development

Pseudoglandular phase – branching morphogenesis

AEC2s Generate AEC1s During Homeostasis and After Injury (→).

- Lung regional pattern formation across gradients of mesenchyme, growth factors, Wnt and Ephrin/Eph concentration.

- Regional differences in cell identity along the lung axis

Lung Regional Differences:

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• Lung regional embryogenesis
• What does prone position ventilation teach us about lung regional differences
• What are the future challenges for optimizing lung regional lung protection in ARDS
What Does PPV Teach Us About Lung Regional Differences

• Improves $\text{PaO}_2/\text{FiO}_2$
• Reduces lung regional overdistension (VILI); cyclic derecruitment (atelectatrazione)
  • Mitigates lung regional cyclic stress-strain heterogeneity
• Improves response to PEEP, recruitment
• Improves RV hemodynamics
  • Augments pulmonary vasodilator responses
• Reduces mortality when applied (early)!
Lung Regional Effects of PPV

- Overdistension
  - Regional V/Q
    - Supine: 1/1, 2/2, 0/3
    - Prone: 2/3, 2/2, 2/1

- Cyclic airspace opening & closing

- End-expiration

- Adapted from RK Albert & C. Guerin

- Dorsal re-expansion
- ↑ gravity-related drainage
- ↑ Perfusion homogeneity
- ↓ Cardiac compression
- ↑ dependent chest wall E’
Prone positioning leads to more homogenous end-expiratory lung volume.

Lung distortion results from:
1. Triangular shape of lung in the ventral-dorsal plane
2. Heart mass
3. Mediastinal mass
4. Ventral/dorsal diaphragm geometry

Preservation of Dorsal PBF in PPV

\[ \triangle \text{Supine} \quad \text{Porcine oleic acid ALI model} \]

- Prone 120m
- Prone 160m

Theoretical recumbent West zones

JC Richard; J Appl Physiol 93:2181–2191
Regional Perfusion Inhomogeneity Ameliorated in PP

T. Richter; AJRCCM 2005
Inhomogeneity in Regional Lung Pressure Impedance

## Salutary Physiological Effects of PPV

<table>
<thead>
<tr>
<th>Physiologic variables</th>
<th>Effect of prone position</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest wall elastance</td>
<td>↑</td>
</tr>
<tr>
<td>Respiratory elastance</td>
<td>↓↑↔ depending on effect on lung elastance</td>
</tr>
<tr>
<td>Lung elastance</td>
<td>↓↑↔ depending on effect on lung recruitment</td>
</tr>
<tr>
<td>Lung recruitment</td>
<td>↑ in dorsal lung areas</td>
</tr>
<tr>
<td>FRC</td>
<td>↑↔ depending on regional lung recruitment</td>
</tr>
<tr>
<td>Pleural pressure</td>
<td>Reduction in ventral-to-dorsal gradient</td>
</tr>
<tr>
<td>Trans-pulmonary P</td>
<td>Follows pleural pressure gradient</td>
</tr>
<tr>
<td>Lung ventilation</td>
<td>Follows trans-pulmonary pressure gradient</td>
</tr>
<tr>
<td>Lung hyperinflation</td>
<td>↓</td>
</tr>
<tr>
<td>Tidal recruitment/derrecruitment</td>
<td>↓ if highly recruitable when supine and receiving high PEEP in the prone</td>
</tr>
<tr>
<td>Tidal hyperinflation</td>
<td>↓ if highly recruitable when supine and receiving high PEEP in the prone</td>
</tr>
</tbody>
</table>
PROSEVA (PROOne in SEvere Ards)

- Severe, persistent ARDS.
- 229 SPV vs. 237 PPV
  - Well matched
- Many contra-indications
- MAP<65 not proned.
- ARDSnet PEEP/FIO2;
  - Low Vt
- Prone duration +/- 17 h
- Lower mortality in PPV

D28 Adj OR: 0.42 (0.26-0.66)  P<.001
D90 Adj OR: 0.48 (0.32-0.72)

C Guérin et al. NEJM 2013;368:2159-2168
Proseva Survival Benefit *Independent of P/F change with PPV at 1 hr*

- Survival unaffected by change in P/F ($P = 0.41$) or change in $\text{Pa}_{\text{CO}_2}$ by quintiles ($P = 0.21$)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Survived (N = 194)</th>
<th>Died (N = 38)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{Pa}_{\text{CO}_2}$, mm Hg</td>
<td>49 ± 14</td>
<td>52 ± 12</td>
<td>0.149</td>
</tr>
<tr>
<td>$\Delta$ from pre–PPV</td>
<td>–0.5 ± 9.4</td>
<td>–2.7 ± 9.1</td>
<td>0.182</td>
</tr>
<tr>
<td>$\text{Pa}_{\text{O}_2}$, mm Hg</td>
<td>119 ± 65</td>
<td>118 ± 59</td>
<td>0.95</td>
</tr>
<tr>
<td>$\Delta$ from pre–PPV</td>
<td>38.9 ± 63</td>
<td>38.8 ± 59</td>
<td>0.987</td>
</tr>
<tr>
<td>P/F, mm Hg</td>
<td>166 ± 83</td>
<td>152 ± 62</td>
<td>0.321</td>
</tr>
<tr>
<td>$\Delta$ from pre–PPV</td>
<td>60 ± 79</td>
<td>55 ± 60</td>
<td>0.618</td>
</tr>
<tr>
<td>P/F increase, mm Hg</td>
<td></td>
<td></td>
<td>0.78</td>
</tr>
<tr>
<td>≥ 20, N (%)</td>
<td>123 (85)</td>
<td>25 (17)</td>
<td></td>
</tr>
<tr>
<td>&lt; 20, N (%)</td>
<td>71 (85)</td>
<td>13 (15)</td>
<td></td>
</tr>
</tbody>
</table>

*RK Albert, AJRCCM 2015*
Prone Ventilation Improves Oxygenation AND Reduces 28d Mortality in Severe ARDS

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PP Events</th>
<th>Total Events</th>
<th>SP Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chan_2007</td>
<td>7</td>
<td>11</td>
<td>7</td>
<td>11</td>
<td>4.9%</td>
<td>1.00</td>
<td>0.53, 1.88</td>
</tr>
<tr>
<td>Curly_2005</td>
<td>4</td>
<td>51</td>
<td>4</td>
<td>50</td>
<td>1.5%</td>
<td>0.98</td>
<td>0.26, 3.71</td>
</tr>
<tr>
<td>Gattinoni_2001</td>
<td>74</td>
<td>152</td>
<td>70</td>
<td>152</td>
<td>11.3%</td>
<td>1.06</td>
<td>0.83, 1.34</td>
</tr>
<tr>
<td>Guerin_2004</td>
<td>134</td>
<td>413</td>
<td>119</td>
<td>378</td>
<td>12.0%</td>
<td>1.03</td>
<td>0.84, 1.26</td>
</tr>
<tr>
<td>Guerin_2013</td>
<td>38</td>
<td>237</td>
<td>75</td>
<td>229</td>
<td>9.1%</td>
<td>0.49</td>
<td>0.35, 0.69</td>
</tr>
<tr>
<td>Mancebo_2006</td>
<td>30</td>
<td>76</td>
<td>32</td>
<td>60</td>
<td>8.7%</td>
<td>0.74</td>
<td>0.51, 1.07</td>
</tr>
<tr>
<td>Taccone_2009</td>
<td>52</td>
<td>168</td>
<td>57</td>
<td>174</td>
<td>9.8%</td>
<td>0.94</td>
<td>0.69, 1.29</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1108</td>
<td>1054</td>
<td>574</td>
<td>982</td>
<td>57.2%</td>
<td>0.86</td>
<td>0.69, 1.07</td>
</tr>
</tbody>
</table>

Total events 339 364
Heterogeneity: Tau² = 0.05, Chi² = 16.87, df = 6 (P = 0.010); I² = 64%
Test for overall effect: Z = 1.33 (P = 0.18)

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OR: 0.79 (0.67-0.94)

SL. Hu; Critical Care. 2014
Prone Ventilation Reduces 28d Mortality Mainly in patients – Longer Durations

SL. Hu; Critical Care. 2014

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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>M-H, Random, 95% CI</td>
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</tr>
<tr>
<td>2.18.1 Duration of PP &gt; 12 h/d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chan_2007</td>
<td>5</td>
<td>11</td>
<td>6</td>
<td>11</td>
<td>5.7%</td>
<td>0.83 [0.36, 1.94]</td>
<td></td>
</tr>
<tr>
<td>Curly_2005</td>
<td>4</td>
<td>51</td>
<td>4</td>
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<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>543</td>
<td>524</td>
<td>58.0%</td>
<td></td>
<td></td>
<td>0.73 [0.54, 0.99]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>129</td>
<td>174</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.05; Chi² = 8.15, df = 4 (P = 0.09); I² = 51%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.05 (P = 0.04)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

| 2.18.2 Duration of PP ≤ 12 h/d |           |       |           |       |        |            |            |
| Gattinoni_2001       | 74        | 152   | 70        | 152   | 20.4%  | 1.06 [0.83, 1.34] |            |
| Guerin_2004          | 134       | 413   | 119       | 378   | 21.6%  | 1.03 [0.84, 1.26] |            |
| Subtotal (95% CI)    | 565       | 530   | 42.0%     |       |        | 1.04 [0.89, 1.22] |            |
| Total (95% CI)       | 1108      | 1054  | 100.0%    |       |        | 0.85 [0.67, 1.06] |            |
| Total events         | 337       | 363   |           |       |        |            |            |
| Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.87); I² = 0% |
| Test for overall effect: Z = 0.52 (P = 0.60) |

PP > 12h/D: OR : 0.73 (0.54-0.99)
PP < 12h/D
PPV Uniquely Mitigates VILI

• Lung regional overdistension (stress/strain) is a key mechanism in the progression of VILI and ALI associated morbidity
  • PPV is regionally lung protective through amplification and dampening of lung stress/strain regulatory pathways.
  • Lung regional mechanisms of VILI are putative therapeutic targets for improving outcome in ALI
Are Lung Regions Different - Ivor S. Douglas MD

400g Male Rats

VT = 18mL/Kg

PEEP 0

4-6 hrs

Park MS, He Q, Edwards MG, Sergew A, Riches DW, Albert RK, Douglas IS. AJRCCM. 2012 186:72-81
Regional Lung Tissue Areas

- Lung tissue – 4 Regions
  - Ventral Cephalad (VCe)
  - Ventral Caudal (VCa)
  - Dorsal Cephalad (DCe)
  - Dorsal Caudal (DCa)
PPV MITIGATES WHOLE LUNG PBEF-1 in High (12mL) and Very High (18mL) vs Low (6mL) VT

- PBEF-1 mRNA expression in whole lung progressively ↑ with incremental VT increases
- Significantly lower expression at each VT, in PPV vs. SPV.
Dorsal Caudal Whole Lung Expression

Unsupervised Clustering Analysis

Multi-dimensional Scaling plot

Prone clusters with Control (non-ventilated)

Park MS, He Q, Edwards MG, Sergew A, Riches DW, Albert RK, Douglas IS. AJRCCM. 2012 186:72-81
Parallel Pathway Analyses; Pathways overrepresented in PP v SP

- MAP kinase activity
- Serine/Threo Phosphatase
- Phosphoprotein phosphatases
- anatomical structure morphogenesis
- cell projections
- cell morphogenesis
- pattern specification processes

Park MS, He Q, Edwards MG, Sergew A, Riches DW, Albert RK, Douglas IS. AJRCCM. 2012 186:72-81
MKP-1/DUSP-1

- 444 genes
  \( P \leq 0.001 \)
- MKP-1 16.6 fold expression in Prone vs. Supine

Park MS, He Q, Edwards MG, Sergew A, Riches DW, Albert RK, Douglas IS. AJRCCM. 2012 186:72-81
PPV stabilizes Dorsal Lung Regional MKP-1/DUSP-1

- 444 genes
  \[ P \leq 0.001 \]
- MKP-1
  16.6 fold expression in Prone vs. Supine

Park MS, He Q, Edwards MG, Sergew A, Riches DW, Albert RK, Douglas IS. AJRCCM. 2012 186:72-81
MAPK-phosphatases (MKP/DUSP)

- 11 dual-specificity phosphatases
  - dephosphorylate MAPKs on regulatory threonine and tyrosine residues
- MKP-1, early response gene; also localizes to nucleus
  - preferentially dephosphorylates activated p38 and JNK relative to ERK in vitro
  - MKP-1-deficient fibroblasts: enhanced sensitivity to apoptosis
- Regulates TNF-α and IL-6 production after LPS
- Negatively regulates endotoxic shock responses, Macrophage activation and type switching
- Insulin responsiveness
- Tumor growth

MKP-1−/− hyperresponsive to LPS – shock
Chi H. et.al. PNAS 2006;103:2274-2279
PPV reduces dorsal lung regional JNK, pP38 activation

Park MS, He Q, Edwards MG, Sergew A, Riches DW, Albert RK, Douglas IS. AJRCCM. 2012 186:72-81
Lung Regional Differences:

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M(urine) ICU – Injurious MV model

SciReq FlexiVent; Continuous SpO2; Continuous EtCO2 and pulse volume

C57/B6 WT

-15min; MRx 0.75mg/kg i.p.

3 – 4 hr MV in “mICU”

Sedation; trach

7mL/kg; 3cm PEEP
21mL/kg; ZEEP

Euthanasia, BAL harvest tissues
MKP-1 -/- : amplified VILI

Park MS, He Q, Edwards MG, Sergew A, Riches DW, Albert RK, Douglas IS. AJRCCM. 2012 186:72-81
MKP-1 -/- : Increased Protein leak and cell count (MP predominant)

Park MS, He Q, Edwards MG, Sergew A, Riches DW, Albert RK, Douglas IS. AJRCCM. 2012 186:72-81
Triptolide/MRx 108

- Diterpenoid triepoxide
  - *Tripterygium wilfordi* Hook f,
    - lei gong teng (Chin. 雷公藤), Thunder God Vine
  - soluble derivative PG490-88 (MRx108) MyeloRx

- MKP-1 antagonistic effects
  - MKP-1 induction by LPS\(^1\)
  - ameliorates experimental chlorine-ALI\(^2\);
  - Triptolide & PG490-88 abrogate bleomycin-associated fibroproliferative ALI\(^3,4\)
  - Effects on alveolar epithelial MKP-1 activity and in regulating regional VILI are not known.
MKP-1 expression: Effects of MRx

(A) Western blot analysis showing MKP-1 and Tubulin expression levels under different conditions:

- PBS High Vt
- PG High Vt
- PG Low Vt

(B) Increased MKP-1 expression in PG High Vt compared to PBS High Vt.

(C) Micrographs showing tissue sections stained with antibodies against MKP-1.

NS indicates no significant difference.

Park MS, He Q, Edwards MG, Sergew A, Riches DW, Albert RK, Douglas IS. AJRCCM. 2012 186:72-81
MRx-108 Ameliorates VILI

Park MS, He Q, Edwards MG, Sergew A, Riches DW, Albert RK, Douglas IS. AJRCCM. 2012 186:72-81
MRx-108 Ameliorates VILI

Park MS, He Q, Edwards MG, Sergew A, Riches DW, Albert RK, Douglas IS. AJRCCM. 2012 186:72-81
MRx regulates MAPK in VILI

Park MS, He Q, Edwards MG, Sergew A, Riches DW, Albert RK, Douglas IS. AJRCCM. 2012 186:72-81
MRx modestly inhibits NFκB

Park MS, He Q, Edwards MG, Sergew A, Riches DW, Albert RK, Douglas IS. AJRCCM. 2012 186:72-81
In vivo MAPK regulation of VILI

Cyclic, Injurious Mechanical Ventilation

Regional Stress/Strain

Prone position

↑ MAPK (p38; JNK)

↓ MKP-1

↓ IκBα

PG490-88 (triptolide)

↑ NF-κB

↓ IL-8 (KC/MIP-2)

Alveolar barrier injury and inflammation

↓ VILI
Now I Know Why……

QUESTIONS?

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for lecture hand-outs