VALI – The next decade: Future of lung protection

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Conflict of Interest

- Apeiron: Consultant
- Asthmatx/Boston Scientific: Chair, DSMB
- Ferring: Chair, DSMB
- Gambro/Baxter: Advisory Board
- Maquet Critical Care: Advisory Board
- Novalung: Advisory Board
- PneumRx: Chair, DSMB
Lung Protection: Current State

- $V_t=6 \text{ ml/kg, PBW}$
- PEEP based on PEEP/Fi$O_2$ table
- $\pm$ Prone position
- $\pm$ Neuromuscular blockers
The Next 10 Years
Personalized Precision Ventilation

LUNG PROTECTION

- Minimize lung stress/strain while removing CO$_2$
- Decrease CO$_2$ that needs to be removed by lungs
Minimize lung stress/strain while removing CO$_2$
Setting the right dose of ventilatory support

“Dose” of Ventilatory Support

Dysfunction

Respiratory Distress
Asynchrony
Optimum
Asynchrony
VILI
VIDD
Effect of Lung Recruitment and Titrated Positive End-Expiratory Pressure (PEEP) vs Low PEEP on Mortality in Patients With Acute Respiratory Distress Syndrome A Randomized Clinical Trial

Hazard ratio, 1.20 (95% CI, 1.01-1.42); P = .041
Minimize lung stress/strain while removing CO$_2$.

Optimize patient control of ventilator strategy.

- Patient control of ventilatory pattern (NAVA, PAV)
Hypothesis
  » Letting a patient “control” Vt will limit VILI

Rationale
  » There are reflexes in the lung that limit tidal volume when lungs get overstretched

Methods
  » Rabbits with tracheal acid instillation
  » 3 groups: 15 ml/kg; 6 ml/kg; NAVA
Results: P/F & Wet/Dry Weight

A

Tidal volume

ml / kg

0 0.5 1 2 3 4 5 6

hours

p (t-g) <0.001

B

Lung wet to dry ratio

Lung wet to dry ratio

0 4 8 12

dependent right lower lobe

non-dependent right lower lobe

Healthy control

VC 15 ml/kg

VC 6 ml/kg

NAVA

p = 0.028

$\dagger$, $\ddagger$
Direct Neural Control of Ventilation

EEG brainwaves

- **Gamma**: Problem Solving, Concentration
- **Beta**: Busy, active mind
- **Omicron**: Respiratory rhythm
- **Theta**: Drowsiness
- **Delta**: Sleep, dreaming

St. Michael's
Inspired Care. Inspiring Science.
Personalized Precision Ventilation

Minimize lung stress/strain while removing CO$_2$

Spontaneous Ventilation
- Optimize patient control of ventilator strategy
  - Patient control of ventilatory pattern (NAVA, PAV)

Controlled Ventilation
- Better phenotyping of patients
  - PEEP
  - $V_t$
  - $\downarrow V_d$

LUNG PROTECTION
Subphenotypes in acute respiratory distress syndrome: latent class analysis of data from two randomised controlled trials

Carolyn S Calfee, Kevin Delucchi, Polly E Parsons, B Taylor Thompson, Lorraine B Ware, Michael A Matthay, and the NHLBI ARDS Network

Differences in response to PEEP strategy by phenotype (ALVEOLI cohort)

<table>
<thead>
<tr>
<th></th>
<th>Phenotype 1 (n=404)</th>
<th>Phenotype 2 (n=145)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low PEEP (n=202)</td>
<td>High PEEP (n=202)</td>
<td></td>
</tr>
<tr>
<td>Mortality at 90 days</td>
<td>33 (16%)</td>
<td>48 (24%)</td>
<td>0.049</td>
</tr>
<tr>
<td>Ventilator-free days</td>
<td>20 (10-25)</td>
<td>21 (3-24)</td>
<td>0.018</td>
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<tr>
<td>Organ failure free-days</td>
<td>22 (11-26)</td>
<td>22 (9-26)</td>
<td>0.003</td>
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<tr>
<td></td>
<td>Low PEEP (n=71)</td>
<td>High PEEP (n=74)</td>
<td></td>
</tr>
<tr>
<td>Mortality at 90 days</td>
<td>36 (51%)</td>
<td>31 (42%)</td>
<td></td>
</tr>
<tr>
<td>Ventilator-free days</td>
<td>2 (0-21)</td>
<td>4.5 (0-20)</td>
<td></td>
</tr>
<tr>
<td>Organ failure free-days</td>
<td>4 (0-18)</td>
<td>6.5 (0-21)</td>
<td></td>
</tr>
</tbody>
</table>
Personalized Precision Ventilation

LUNG PROTECTION

Minimize lung stress/strain while removing CO₂

Spontaneous Ventilation

Optimize patient control of ventilator strategy

• Patient control of ventilatory pattern (NAVA, PAV)

Controlled Ventilation

↓ ΔP

• PEEP
• Vt
• ↓ Vd
Driving Pressure and Survival in the Acute Respiratory Distress Syndrome

Marcelo B.P. Amato, M.D., Maureen O. Meade, M.D., Arthur S. Slutsky, M.D., Laurent Brochard, M.D., Eduardo L.V. Costa, M.D., David A. Schoenfeld, Ph.D., Thomas E. Stewart, M.D., Matthias Briel, M.D., Daniel Talmor, M.D., M.P.H., Alain Mercat, M.D., Jean-Christophe M. Richard, M.D., Carlos R.R. Carvalho, M.D., and Roy G. Brower, M.D.

- **Current:**
  - $V_t = 6 \text{ ml/kg PBW}$

- **Future:** Individualize $V_t$ to patient’s underlying disease process
  - Driving pressure $\Delta P = P_{\text{plat}} - \text{PEEP}$
  - $C_{RS} = \frac{V_t}{(P_{\text{plat}} - \text{PEEP})}$

\[ \Delta P = \frac{V_t}{C_{RS}} \]
Personalized Precision Ventilation

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- **Controlled Ventilation**
  - ↓ ΔP OR ↓ Power
    - PEEP
    - Vt
    - ↓ Vd

Decrease CO$_2$ that needs to be removed by lungs

↓ Total metabolic CO$_2$ production:
- Hypothermia
- Drugs
H₂S: potent, reversible inhibitor of cytochrome c oxidase, the terminal enzyme complex in electron transport chain

Hypothesis: H₂S will reduce metabolic rate, and core body temperature

Regulated hypometabolic states may be beneficial for I/R injury, organ preservation, and decreasing VILI
H₂S Induces a Suspended Animation–Like State in Mice

Eric Blackstone,¹,² Mike Morrison,² Mark B. Roth²*

A

[Graph showing carbon dioxide production and oxygen consumption at different time points: -5 minutes, +5 minutes, +6 hours, +1 hour recovery.]

- Black bars: Carbon Dioxide Production
- Gray bars: Oxygen Consumption
BUYING TIME IN SUSPENDED ANIMATION

An ability to put the human body on hold could safeguard the critically injured or preserve donor organs for transport. Does the power to reversibly stop our biological clocks already lie within us? 

By Mark B. Roth and Todd Nystul
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ECLS
- ECMO
ECMO criteria for influenza A (H1N1)-associated ARDS: role of transpulmonary pressure


Patients with influenza A (H1N1) induced ARDS
N = 20

Patients transferred to regional center for ECMO
N = 14

Partitioning of respiratory mechanics

Oxygenation Index: 34 ± 5
P_{PLAT_L}: 27.2 ± 1.2 cmH_2O
N = 7
ECMO

Oxygenation Index: 37 ± 4
P_{PLAT_L}: 16.6 ± 2.9 cmH_2O
N = 7

INCREASE PEEP UNTIL P_{PLAT_L} ≥ 25 cmH_2O

Oxygenation Index: 16 ± 1

NO ECMO

6/7 survived
Minimize lung stress/strain while removing CO₂

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**ECLS**
- ECMO
- ECCO₂R

Personalized Precision Ventilation
Key Issue: How do predict patients most likely to benefit from ECCO$_2$R?
GOAL:
- Use physiological parameters to identify patients most likely to have a major decrease in stress/strain due to ECCO$_2$R
Assumptions

- $V_{d,anat}$: Relatively constant in any given individual; independent of $V_t$

- $\frac{V_{d,alv}}{V_t} = \text{Constant, independent of } V_t$

Decrease in $\Delta P = \frac{-k}{C_{stat,RS} \cdot \left(1 - \frac{V_{d,alv}}{V_t}\right) \cdot F_R \cdot P_{aCO_2} \cdot \dot{V}_{CO_2,ECML}}$
Predicted Decrease in Mortality with ECCO$_2$R* as function of $C_{RS}$ and $V_{d,alv}$

*Assuming CO$_2$ removal of 80 ml/min by ECCO$_2$R

Goligher, Amato, Slutsky. *Am J Resp Crit Care Med.* 2017 Sep 1;196:558-568
Personalized Precision Ventilation

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**Controlled Ventilation**
- **↓ ΔP**
- **↓ Power**
  - PEEP
  - Vt
  - ↓ Vd

**↓ metabolic CO\(_2\) production:**
- Hypothermia
- Drugs

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**ECLS**
- ECCO\(_2\)R
- ECMO
- Ex vivo & in vivo lung support
Functional Repair of Human Donor Lungs by IL-10 Gene Therapy

Marcelo Cypel,1,2 Mingyao Liu,1,2 Matt Rubacha,1 Jonathan C. Yeung,1,2 Shin Hirayama,1,2 Masaki Anraku,1,2 Masaaki Sato,1,2 Jeffrey Medin,3 Beverly L. Davidson,4 Marc de Perrot,1,2 Thomas K. Waddell,1,2 Arthur S. Slutsky,5,6 Shaf Keshavjee1,2*


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Diagram of lung perfusion system.
**In vivo lung perfusion**

Possible pulmonary therapies for isolated in vivo lungs
- High dose lung-specific IV antibiotics
- Lung specific gene therapy
- High dose anti-inflammatory
- Stem cells
- “Scrub the lungs”

In vivo lung perfusion

V-A ECMO
Conclusions

- Currently, we have reasonably good lung protective strategies
  - Room for improvement
- Personalized precision ventilation (PPV) is the future of lung protection
  - Better phenotyping
    - Biologic, imaging, physiologic
  - More physiology, physiology, physiology
The Future