How Ventilators Injure Lungs

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Conflicts of Interest

- Patent applied for ventilation device
- No financial conflict of interest with the subject matter of this talk
Research Support

- Dr Geoffrey Barker Chair in Critical Care Research
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1. Atelectasis
2. Genes
3. Circulating Mediators
4. Age
5. Novel Enzymes
6. NET formation
7. Local Propagation
8. CO$_2$ ...
1. Atelectasis
Atelectasis Causes Vascular Leak and Lethal Right Ventricular Failure in Uninjured Rat Lungs

Michelle Duggan, Conán L. McCaul, Patrick J. McNamara, Doreen Engelberts, Cameron Ackerley, and Brian P. Kavanagh
Atelectasis Causes Vascular Leak and Lethal Right Ventricular Failure in Uninjured Rat Lungs

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After Recruitment

Am J Respir Crit Care Med 2003
In atelectasis, *where* does the injury occur?

Non-Dependent (Aerated)

Dependent (Atelectatic)
Atelectasis Causes Alveolar Injury in Nonatelectatic Lung Regions

Shinya Tsuchida, Doreen Engelberts, Vanya Peltekova, Natalie Hopkins, Helena Frndova, Paul Babyn, Colin McKerlie, Martin Post, Paul McLoughlin, and Brian P. Kavanagh
Atelectasis causes tidal volume to be distributed to aerated regions:

- Overstretch
- Inflammation
2. Genes
Early Changes in Lung Gene Expression due to High Tidal Volume

Ian B. Copland, Brian P. Kavanagh, Doreen Engelberts, Colin McKerlie, Jaques Belik, and Martin Post

Am J Respir Crit Care Med 2003
What happens if Egr1 Gene Deleted?
Early Growth Response-1 Worsens Ventilator-induced Lung Injury by Up-Regulating Prostanoid Synthesis

Nicola Ngiam1*, Vanya Peltekova1*, Doreen Engelberts1*, Gail Otulakowski1, Martin Post1, and Brian P. Kavanagh1,2,3

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Compliance Impairment

Control: No Blocker
At least some genes are over (or under) expressed in lung injury:

- **Inhibit** injurious products
- **Augment** protective products
3. Circulating Mediators
Lung-derived soluble mediators are pathogenic in ventilator-induced lung injury

Thomas Jaecklin, Doreen Engelberts, Gail Otulakowski, Hugh O’Brodovich, Martin Post, and Brian P. Kavanagh

Non-Recirculating Perfusate
Lung-derived soluble mediators are pathogenic in ventilator-induced lung injury

Thomas Jaecklin,1 Doreen Engelberts,1 Gail Otulakowski,1 Hugh O’Brodovich,2 Martin Post,1 and Brian P. Kavanagh1,2

Non-Recirculating Perfusate

Recirculating Perfusate
Lung-derived soluble mediators are pathogenic in ventilator-induced lung injury

Thomas Jaecklin,1 Doreen Engelberts,1 Gail Otulakowski,1 Hugh O’Brodovich,3 Martin Post,1 and Brian P. Kavanagh1,2
Confirmation by ‘Transplantation’

- Ventilate with High or Low $V_T$
- Collect & store perfusate
- Use it *next day* – Low $V_T$ ventilation
Lung-derived soluble mediators are pathogenic in ventilator-induced lung injury

Thomas Jaecklin,1 Doreen Engelberts,1 Gail Otulakowski,1 Hugh O’Brodovich,3 Martin Post,1 and Brian P. Kavanagh1,2
Circulating mediators cause injury:

- Inhibit, antagonize
- Remove
4. Age
High Tidal Volume Ventilation Causes Different Inflammatory Responses in Newborn versus Adult Lung

Ian B. Copland, Francisco Martinez, Brian P. Kavanagh, Doreen Engelberths, Colin McKerlie, Jaques Belik, and Martin Post

Mediator Responses
Adult > Infant

Am J Respir Crit Care Med 2004
Lung Development and Susceptibility to Ventilator-induced Lung Injury

Alik Kornecki, Shinya Tsuchida, Hari Kumar Ondiveeran, Doreen Engelberts, Helena Frndova, A. Keith Tanswell, Martin Post, Colin McKerlie, Jaques Belik, Alison Fox-Robichaud, and Brian P. Kavanagh
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Adult

Expiration

Inspiration
5. Novel Enzymes
Hypercapnia attenuates ventilator-induced lung injury via a disintegrin and metalloprotease-17

Gail Otulakowski¹, Doreen Engelberts¹, Galina A. Gusarova³, Jahar Bhattacharya³, Martin Post¹ and Brian P. Kavanagh¹,²

Sheddase in Action

![Images showing Calcein, TNFR1 BL 0min, and TNFR1 BL 60min under normocapnia baseline conditions.](image-url)
Blocking Sheddase – *in vivo*

Protein Leak

![Graph showing protein leak comparison between Vehicle and TAPI 2 treatment groups.](image-url)
Sheddase contributes to VILI and can potentially be inhibited
6. Neutrophil NETs
Mechanical Ventilation Induces Neutrophil Extracellular Trap Formation

Citrullinated Histone co-localized with DNA in lung injury...  
BUT... blockade of NET formation - no impact on injury

High V_T + Vehicle  
High V_T + LPS

Citrullinated Histone

Citrullinated Histone + DNA

Anesthesiology 2015
NETS occur in VILI but do not contribute to the injury
7. Local Propagation
Acid Aspiration
Visualizing the Propagation of Acute Lung Injury

Maurizio Cereda, M.D., Yi Xin, M.S., Natalie Meeder, B.A., Johnathan Zeng, B.S.E., YunQing Jiang, M.S.E., Hooman Hamedani, M.S., Harrilla Profka, D.V.M., Stephen Kadlecak, Ph.D., Justin Clapp, Ph.D., Charuhas G. Deshpande, M.D., Jue Wu, Ph.D., James C. Gee, Ph.D., Brian P. Kavanagh, M.B., Rahim R. Rizi, Ph.D.

No Primary Injury
8. CO$_2$
CO₂ Protects against VILI

Lungs ± CO₂ → Extract mRNA → Gene Array → αTTP

Otulakowski et al, Submitted
α-Tocopherol Transfer Protein Mediates Protective Hypercapnia in Ventilator-Induced Lung Injury
G Otulakowski, D Engelberts, H Arima, H Hirate, H Bayir, M Post, BP Kavanagh

αTTP – ↑Expression, ↑CO₂ Protection

![Graph showing the relationship between αTTP expression and injury](image_url)
α-Tocopherol Transfer Protein Mediates Protective Hypercapnia in Ventilator-Induced Lung Injury
G Otulakowski, D Engelberts, H Arima, H Hirate, H Bayir, M Post, BP Kavanagh

αTTP – No Gene, No Protection

![Graph showing the effect of hypercapnia on injury in αTTP-transferred and non-transferred mice. The graph compares the injury (compliance decrement) in normocapnia and hypercapnia conditions. The αTTP +/+ mice show a significant reduction in injury compared to the αTTP −/− mice under hypercapnia.]
Conclusions ...

Prevent/Reverse Atelectasis
Inhibit/Augment Gene Products
Remove/Inhibit Circulating Mediators
Remain young (or old)
Block Sheddase
(Don’t block) NETs
Understand Local Propagation ... and CO$_2$
Thank You

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