How Ventilators Injure Lungs

Brian Kavanagh

Hospital for Sick Children

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Conflicts of Interest

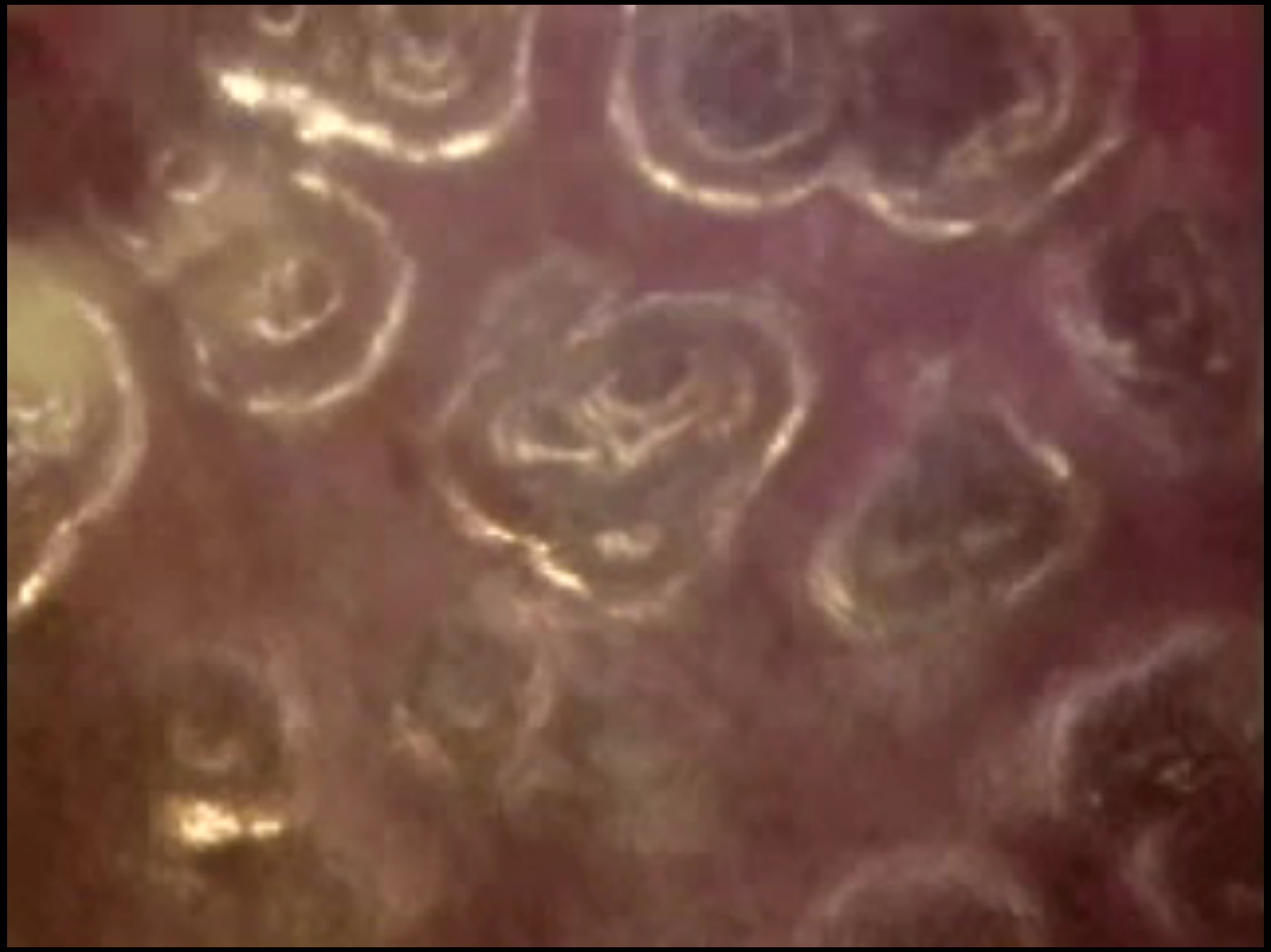
No financial conflict of interest with the subject matter of this talk

Research Support

- Dr Geoffrey Barker Chair in Critical Care Research
- 2 Operating Grants - CIHR

1. Atelectasis
2. Genes
3. Circulating Mediators
4. Age
5. Novel Enzymes
6. NET formation
7. Local Factors

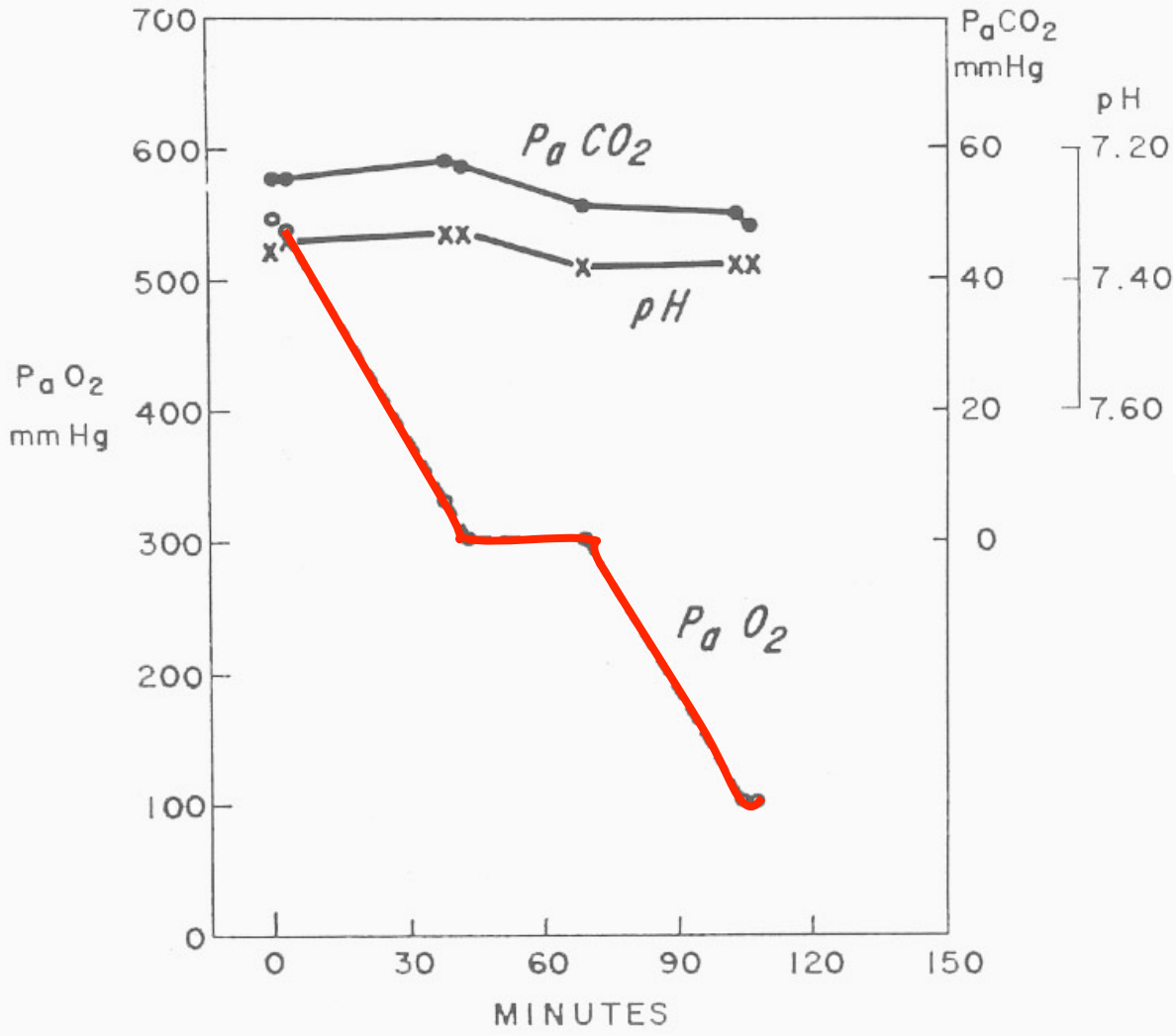
1. Atelectasis



Halter et al, *Am J Respir Crit Care Med* 2003

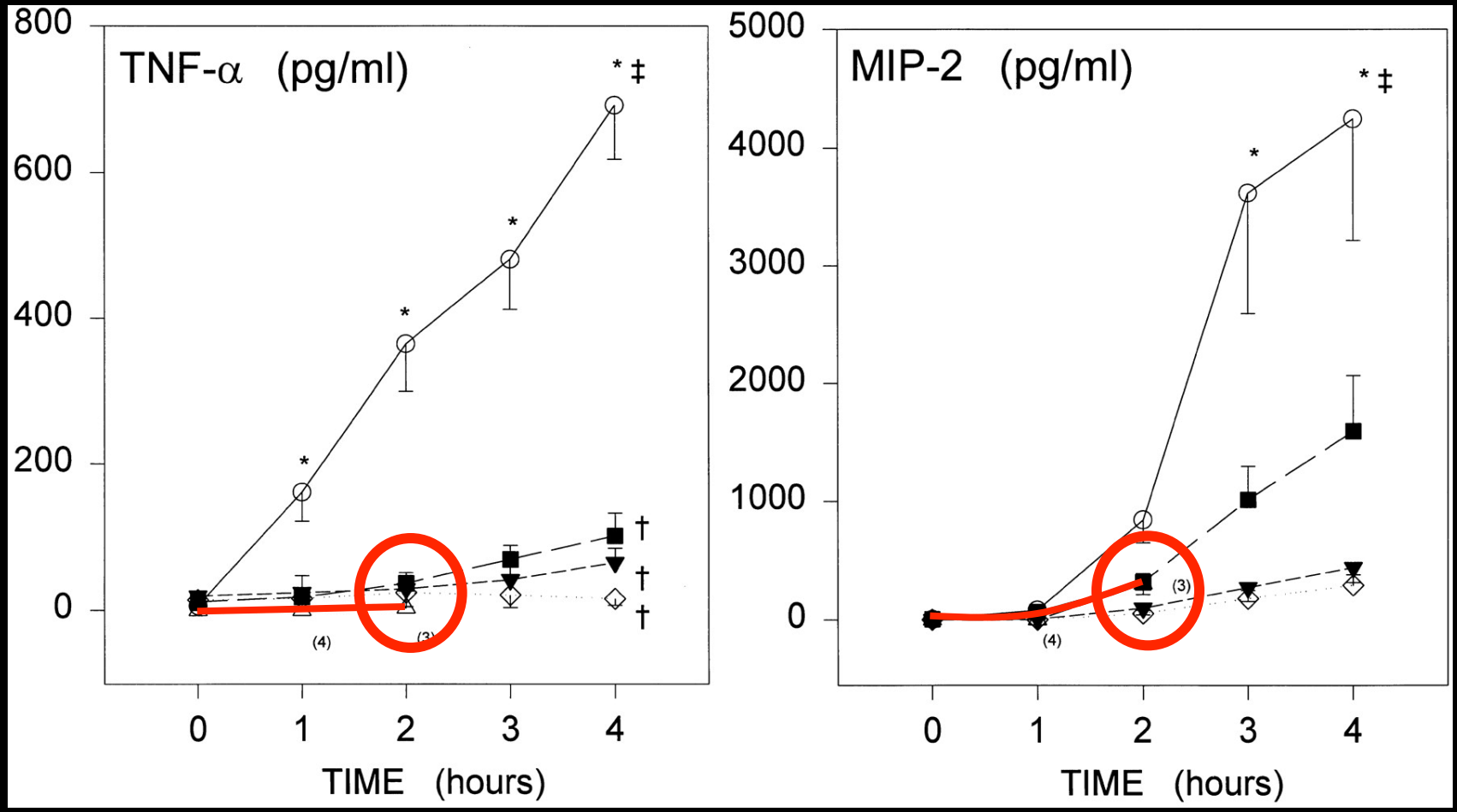
The New England

Journal of Medicine



Bendixen et al.
***N Engl J Med* 1963**

Atelectasis, Cytokines & Injury



Hi V_T, Low PEEP → High Circulating Mediators

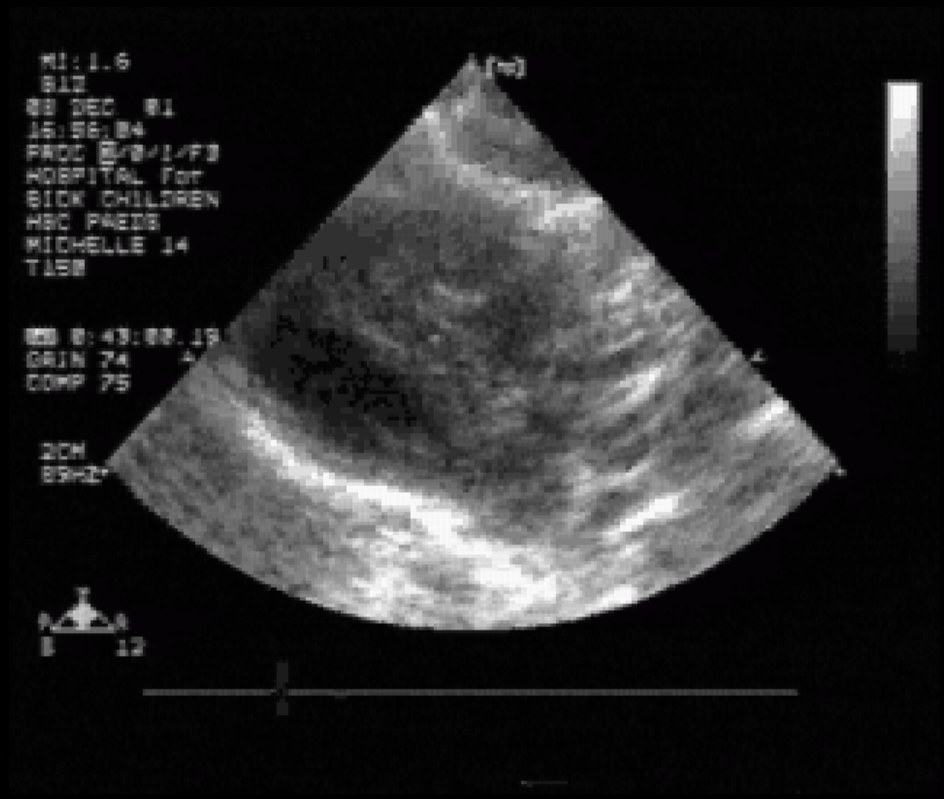
BUT: Low V_T, Low PEEP → High Mortality

Chiumello et al, *AAJRCCM* 1999

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

Before Recruitment



Am J Respir Crit Care Med 2003

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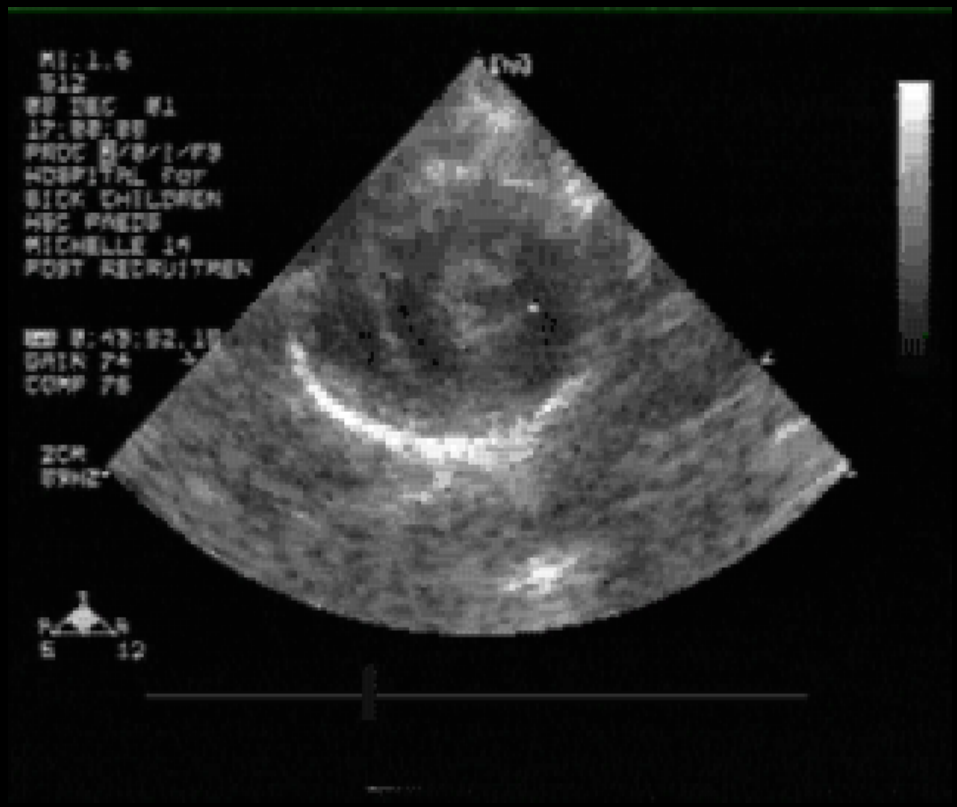
After Recruitment



Am J Respir Crit Care Med 2003

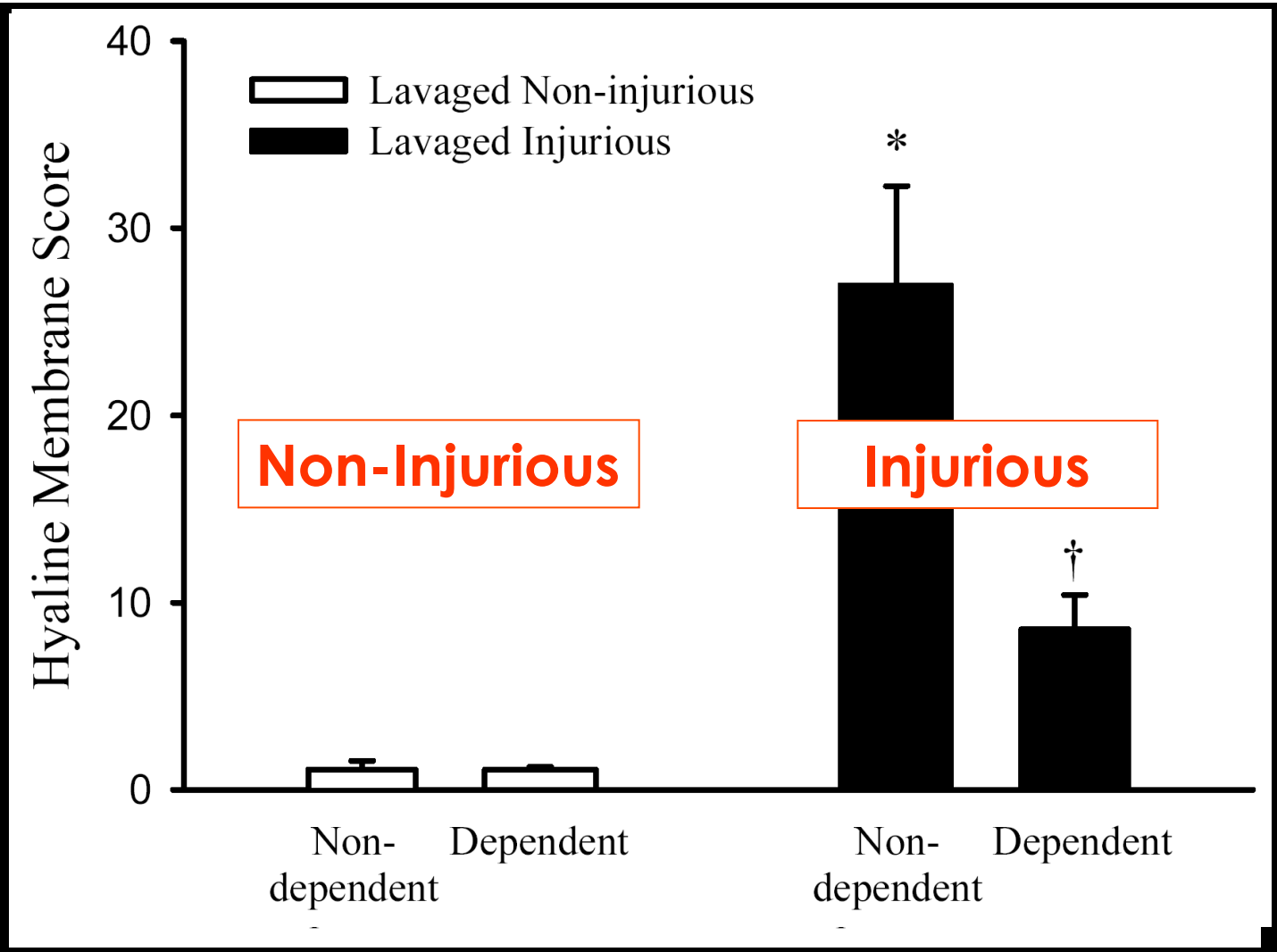
Non-Dependent (Aerated)

Dependent (Atelectatic)

In atelectasis, *where* does the injury occur?

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



Am J Respir Crit Care Med 2006

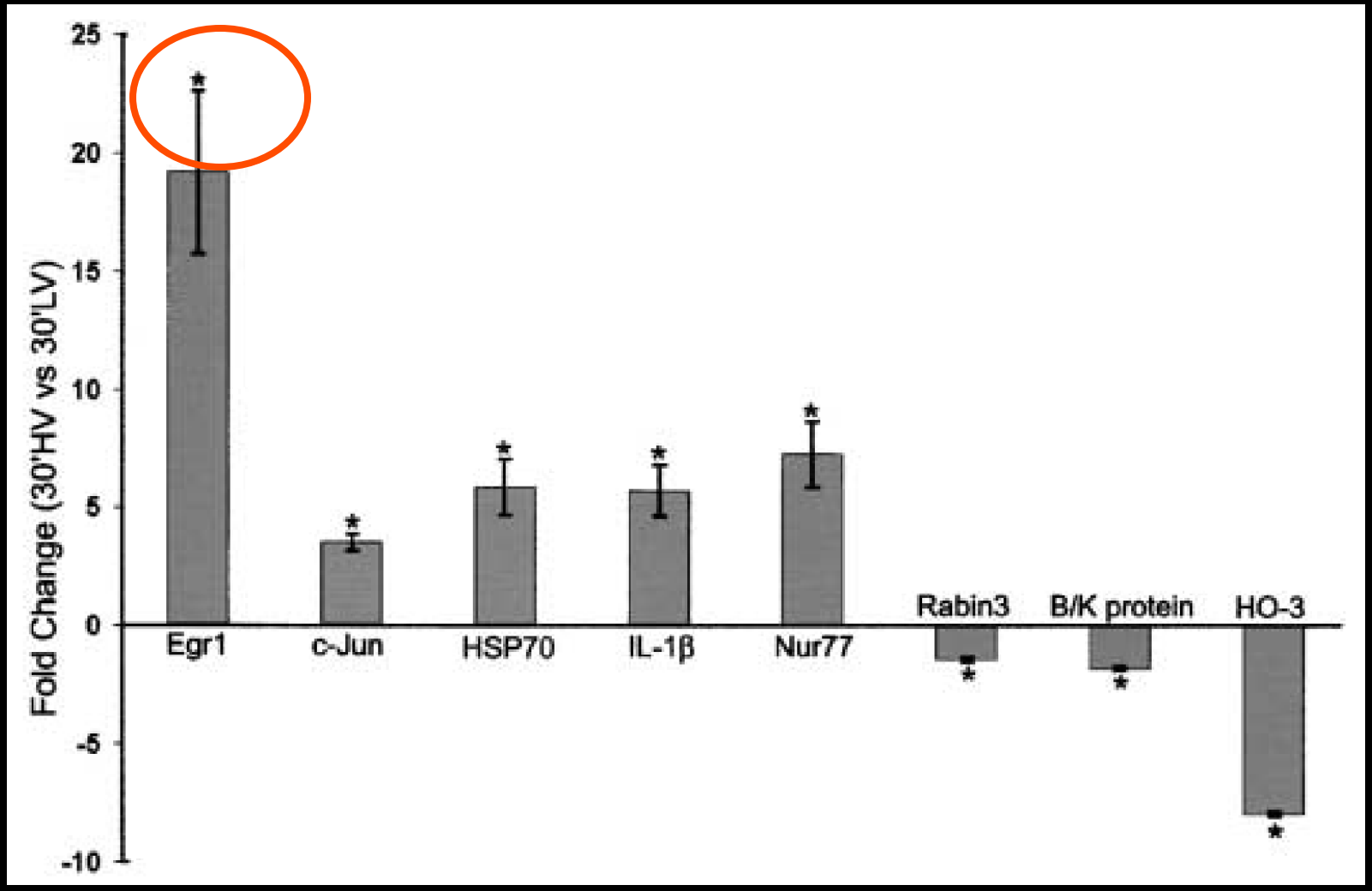
Atelectasis causes tidal volume to be distributed to aerated regions:

- 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

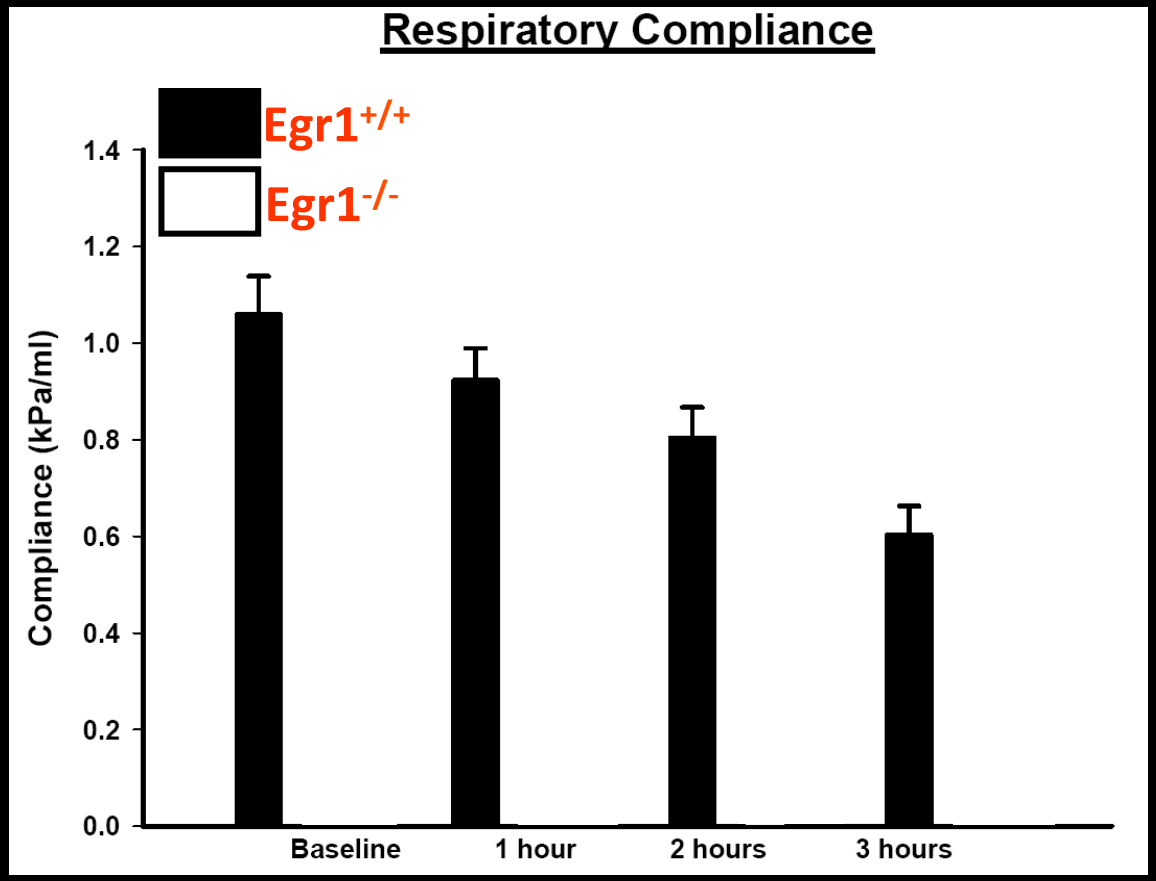


Am J Respir Crit Care Med 2003

Early Growth Response-1 Worsens Ventilator-induced Lung Injury by Up-Regulating Prostanoid Synthesis

Nicola Ngiam[1]*, Vanya Peltekova[1]*, Doreen Engelberts[1], Gail Otulakowski[1], Martin Post[1], and Brian P. Kavanagh[1,2,3]

What happens if Egr1 Gene Deleted?



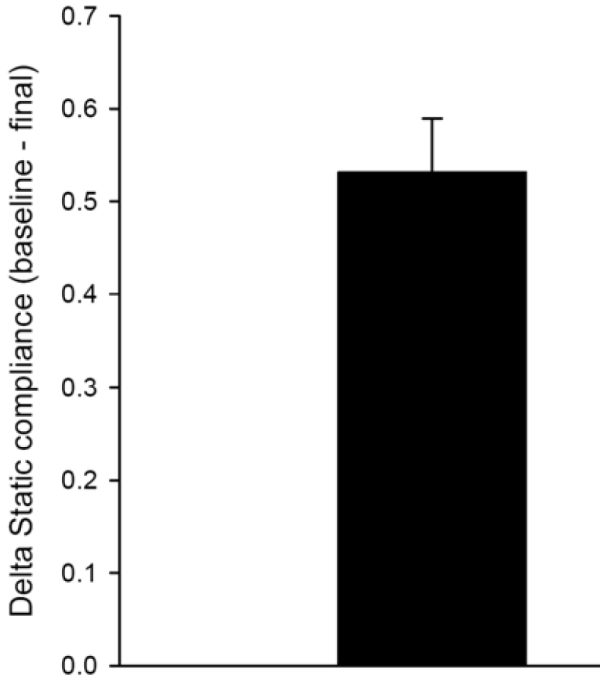
Ngiam *et al*, AJRCCM 2010

Early Growth Response-1 Worsens Ventilator-induced Lung Injury by Up-Regulating Prostanoid Synthesis

Nicola Ngiam[1]*, Vanya Peltekova[1]*, Doreen Engelberts[1]*, Gail Otulakowski[1], Martin Post[1], and Brian P. Kavanagh[1,2,3]

[1]Physiology and Experimental Medicine, [2]Department of Critical Care Medicine, and [3]Department of Anesthesia, Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada

Compliance Impairment



Control: No Blocker

AJRCCM 2010

At least some genes are over (*or under*) expressed in lung injury:

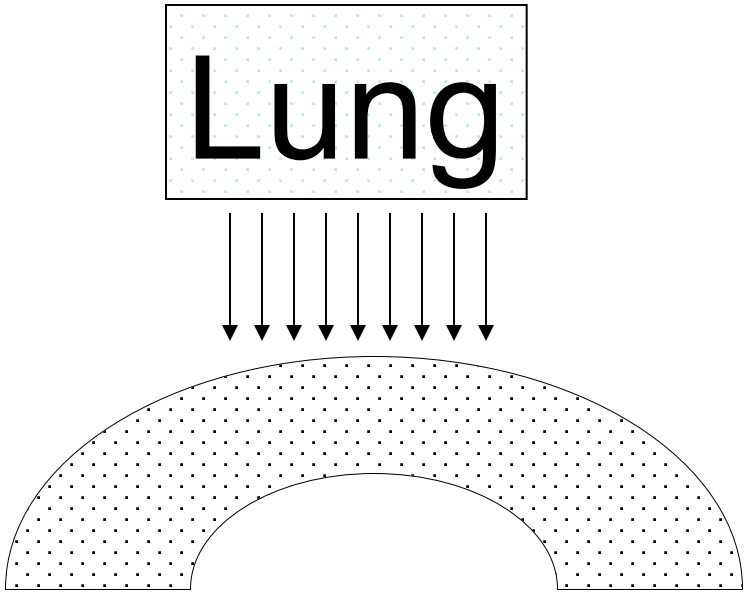
- ***Inhibit*** **injurious products**
- ***Augment*** **protective products**

3. Circulating Mediators

Am J Physiol Lung Cell Mol Physiol 300: L648–L658, 2011.
First published January 14, 2011; doi:10.1152/ajplung.00305.2010.

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. Kavanagh[1,2]



Non-Recirculating Perfusate

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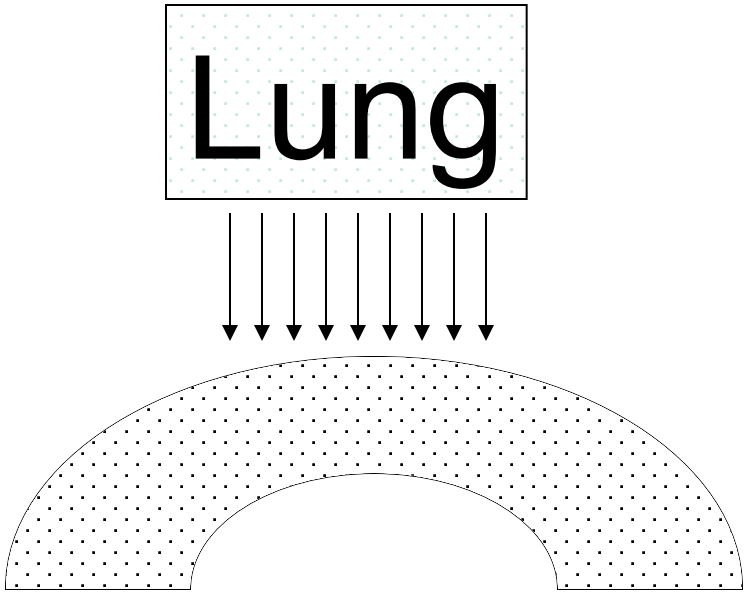

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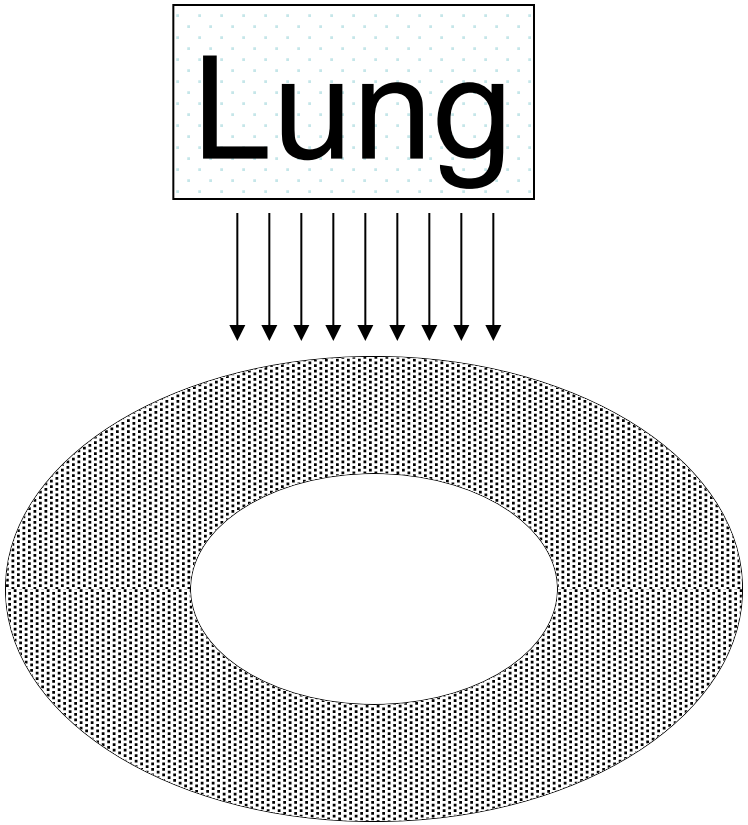

Recirculating Perfusate

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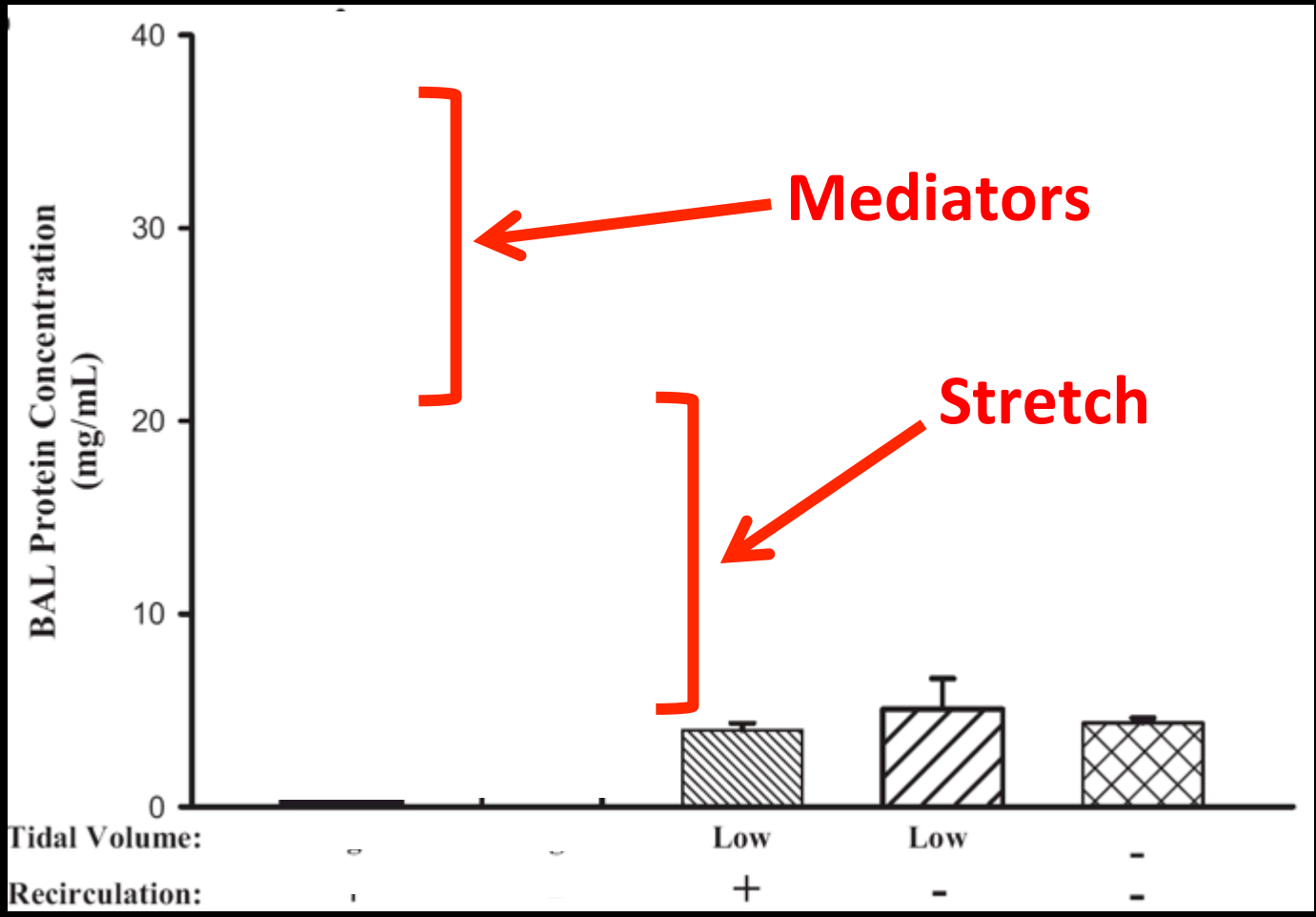

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Confirmation by 'Transplantation'

- Ventilate with High or Low V_T
- Collect & store perfusate
- Use it *next day* – Low V_T ventilation

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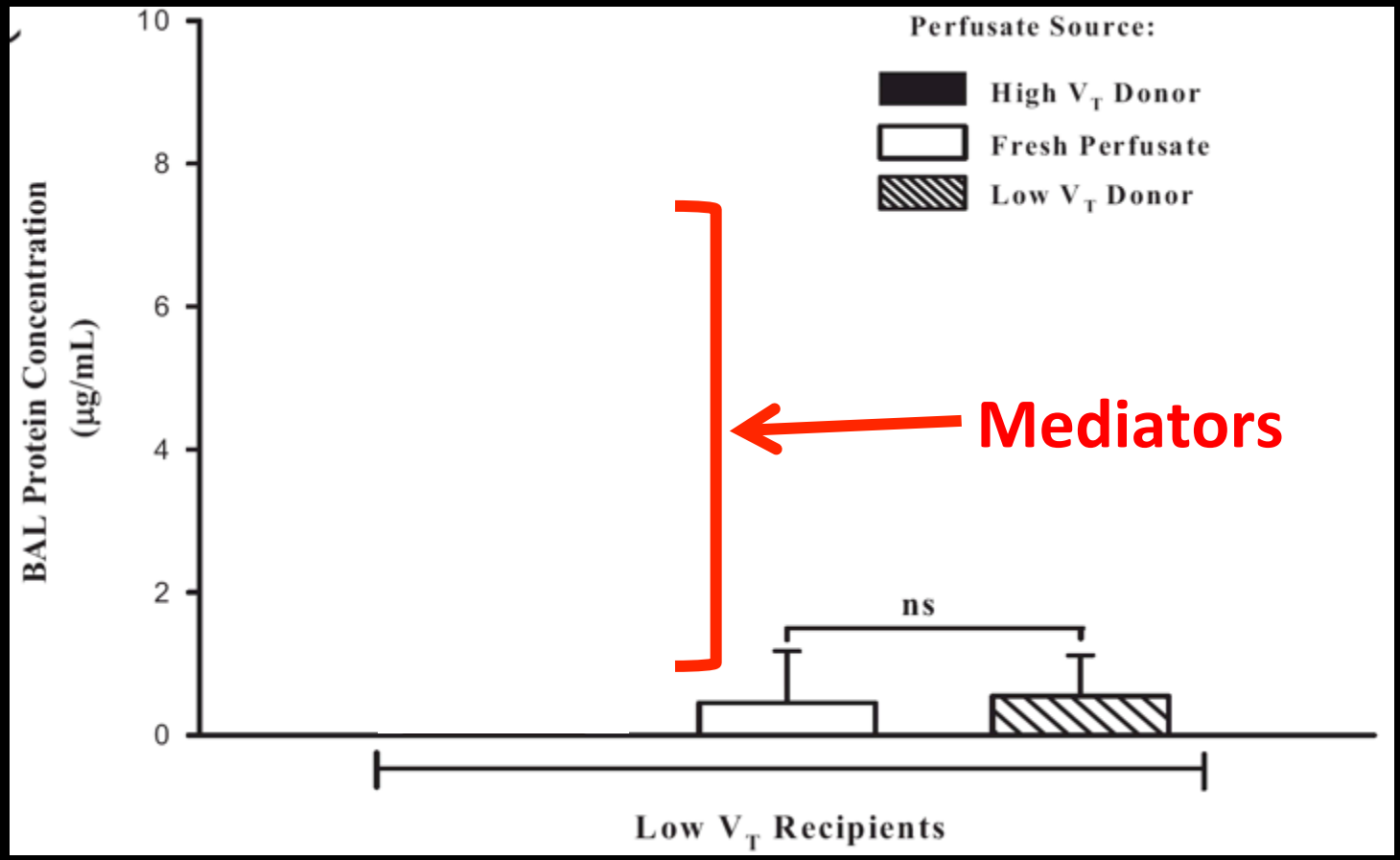


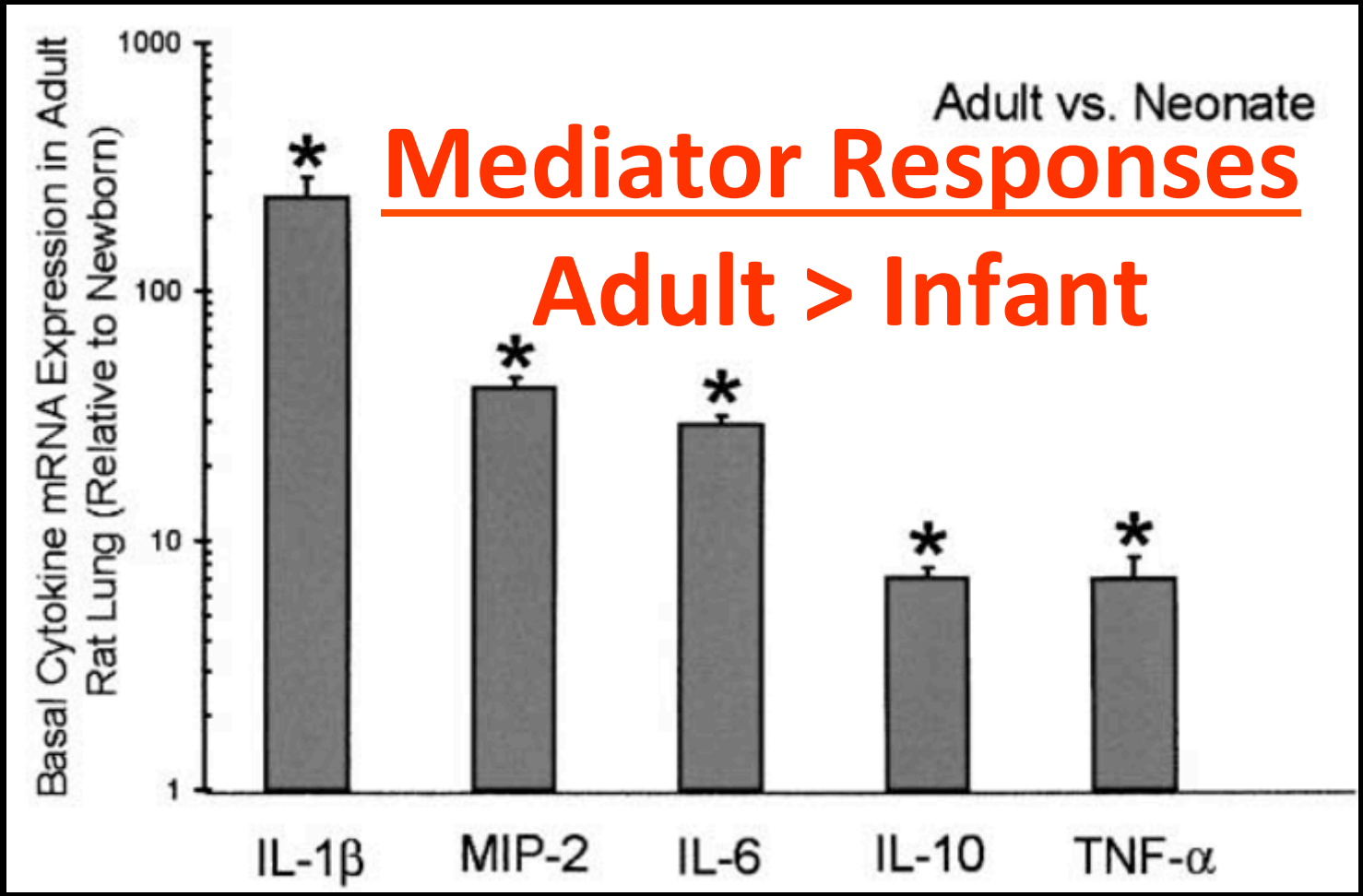
Circulating mediators cause injury:

- **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 Engelberts, Colin McKerlie, Jaques Belik, and Martin Post



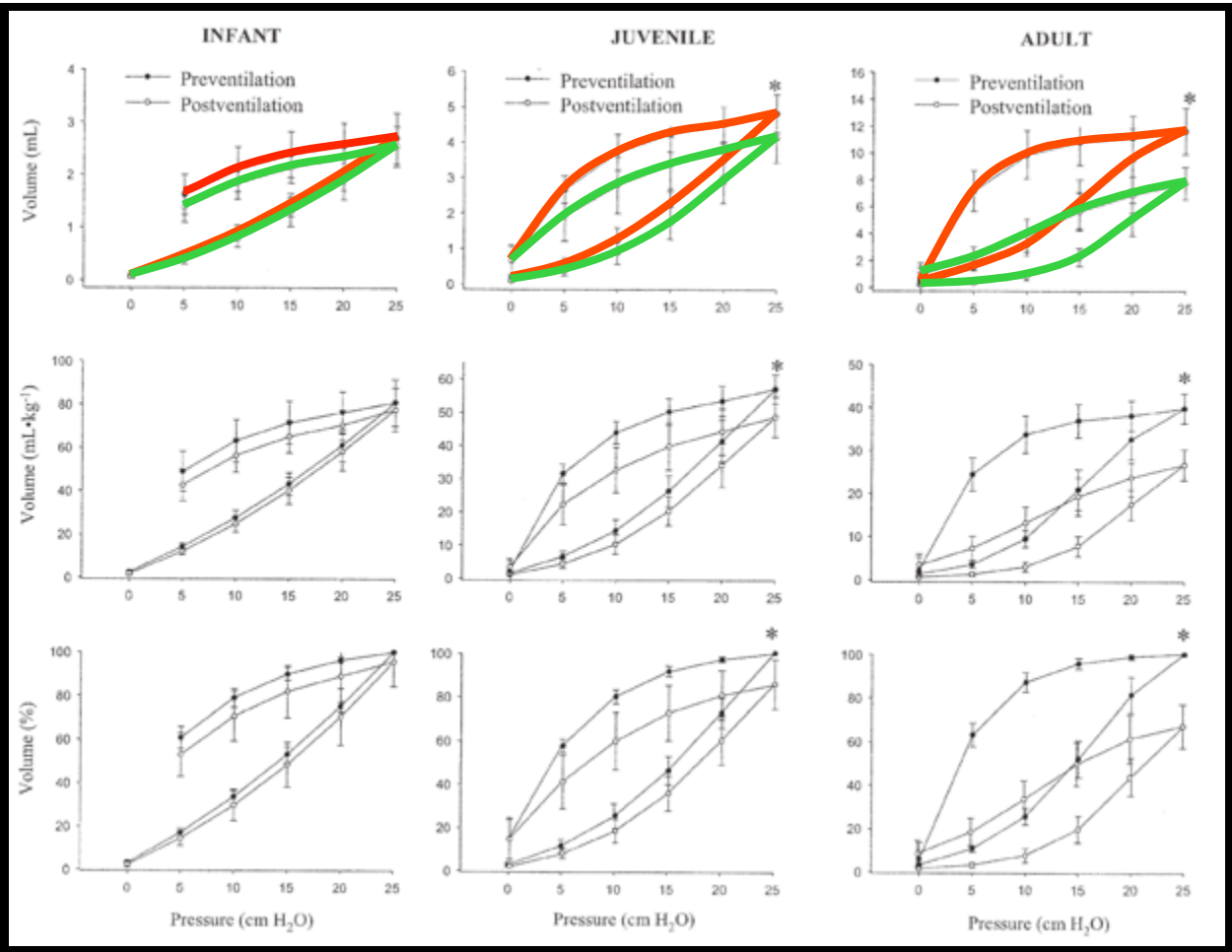
Mediator Responses

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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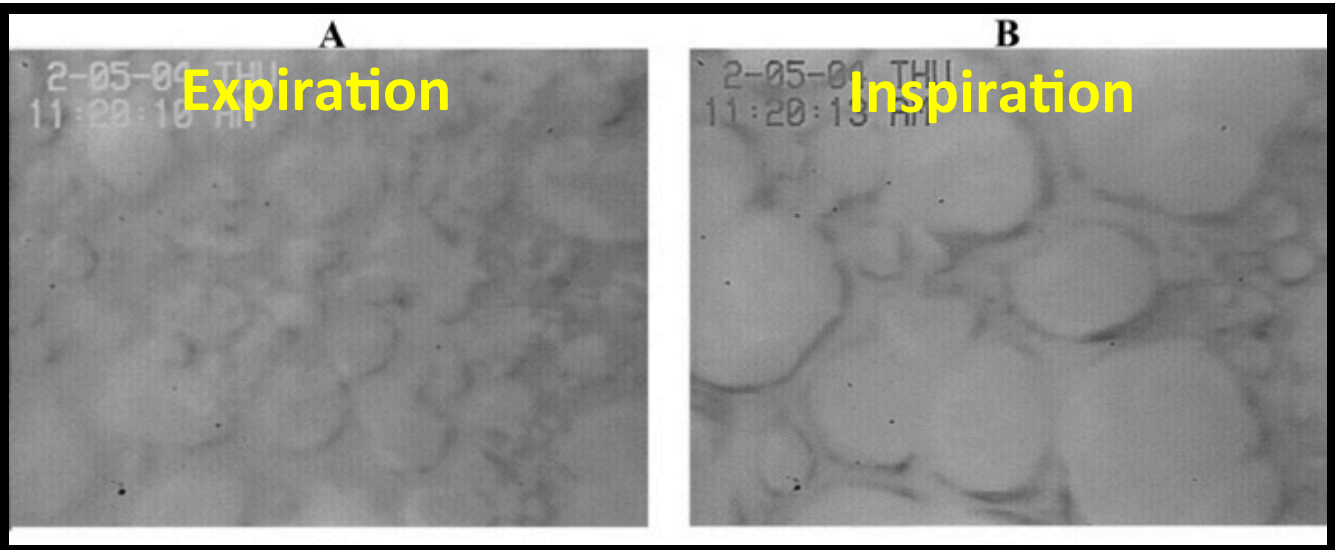
Adult



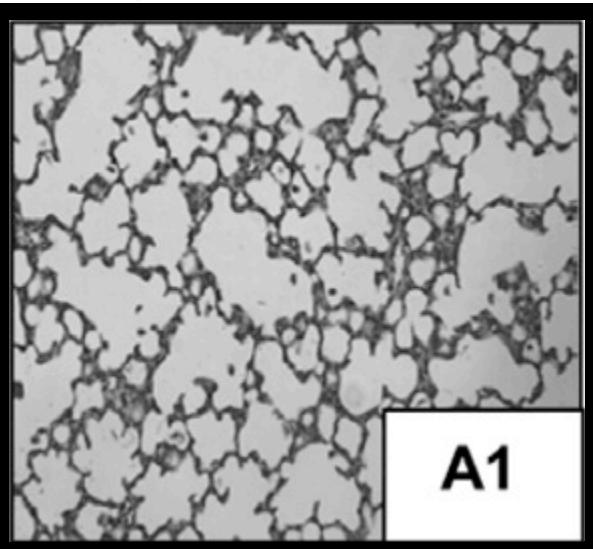
Am J Respir Crit Care Med 2005

The very young …

Prolonged Mechanical Ventilation Induces Cell Cycle Arrest in Newborn Rat Lung

Andreas A. Kroon[1,5], Jinxia Wang[1], Brian Kavanagh[1,3,4], Zhen Huang[1], Maciej Kuliszewski[1], Johannes B. van Goudoever[5,6,7], Martin Post[1,2,3]*

Day7 Control



PLoSOne 2011

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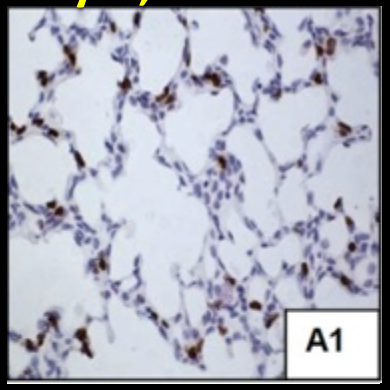
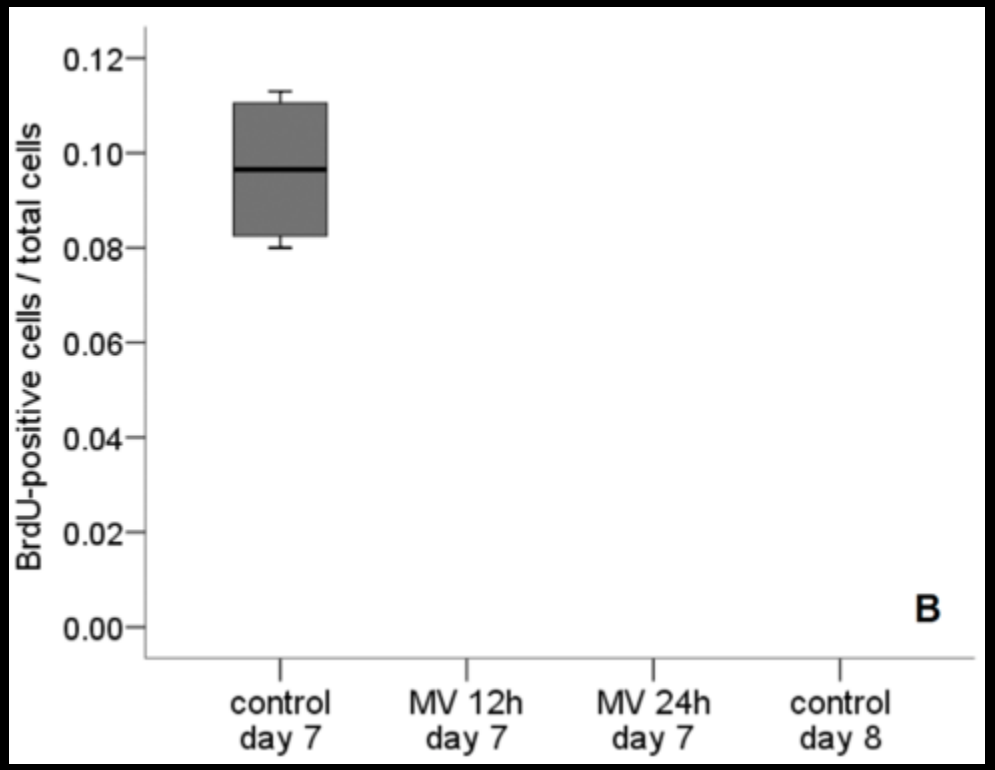
Why does Mechanical Ventilation inhibit Alveolar Development?

… BrdU Staining

Day-7, Control





PLoSOne 2011

Lower age is good for you

- Less injury
- BUT, more impact on development

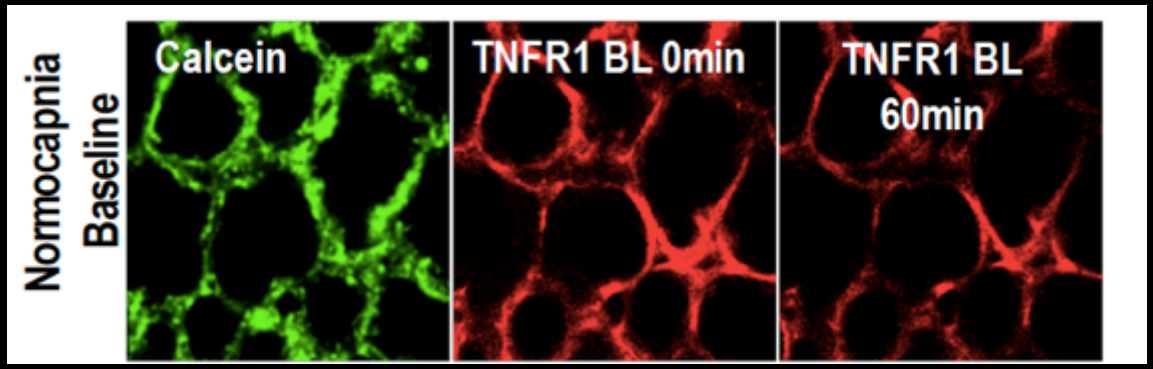
Can't 'stay young' … can learn from the age-differences

5. Novel Enzymes

Hypercapnia attenuates ventilator-induced lung injury via a disintegrin and metalloprotease-17

Gail Otulakowski[1], Doreen Engelberts[1], Galina A. Gusarova[3], Jahar Bhattacharya[3], Martin Post[1] and Brian P. Kavanagh[1,2]

Sheddase in Action



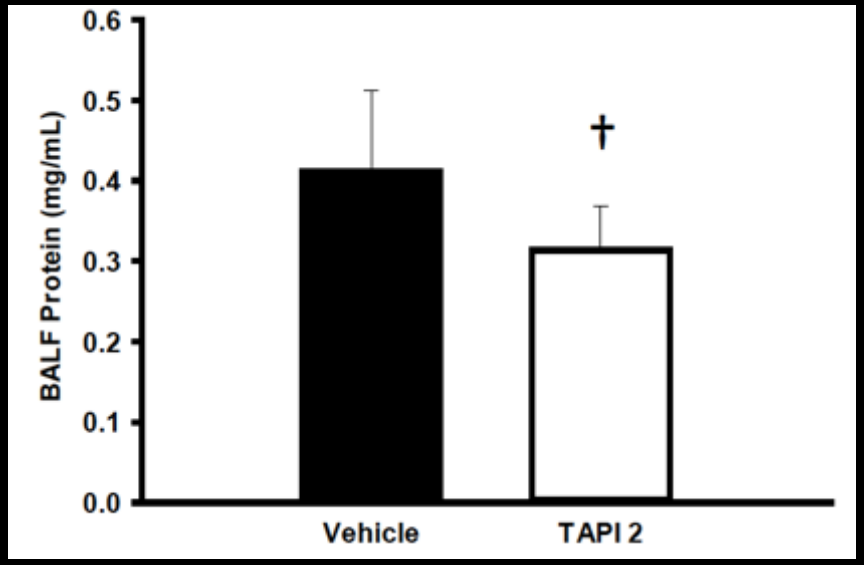
J Physiol 2014

Hypercapnia attenuates ventilator-induced lung injury via a disintegrin and metalloprotease-17

Gail Otulakowski[1], Doreen Engelberts[1], Galina A. Gusarova[3], Jahar Bhattacharya[3], Martin Post[1] and Brian P. Kavanagh[1,2]

Blocking Sheddase – *in vivo*

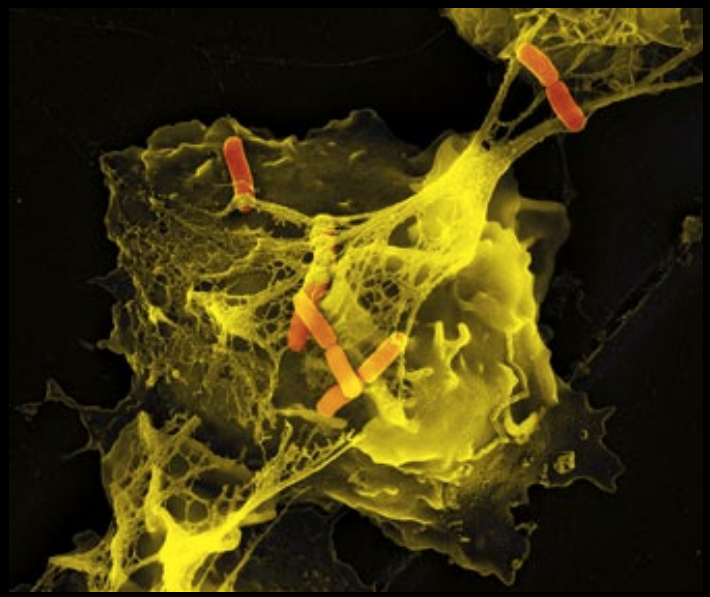
Protein Leak



J Physiol 2014

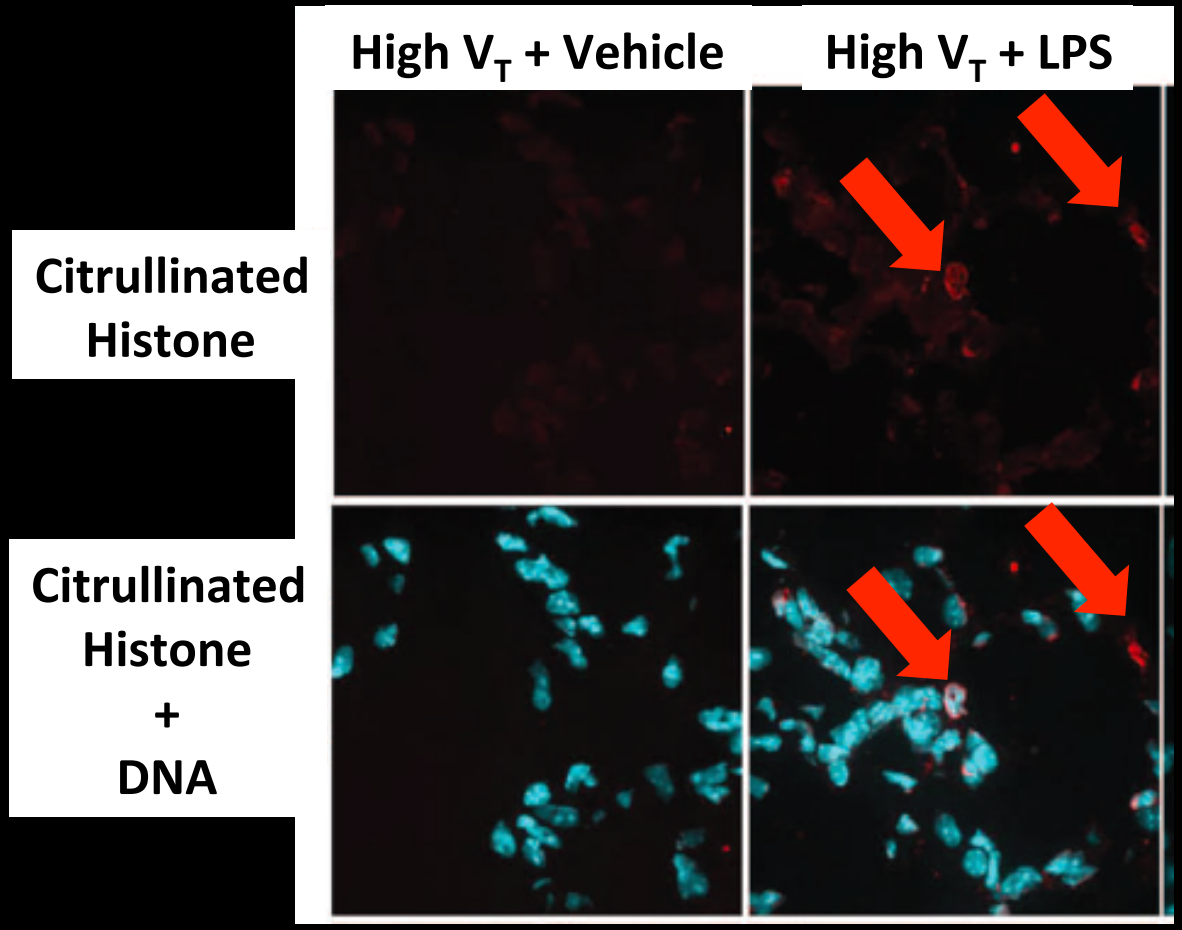
Sheddase contributes to VILI and can potentially be inhibited

6. Neutrophil NETs



Mechanical Ventilation Induces Neutrophil Extracellular Trap Formation

Christopher Yildiz, M.Sc., Nades Palaniyar, M.Sc., Ph.D., Gail Otulakowski, Ph.D., Meraj A. Khan, M.Sc., Ph.D., Martin Post, Ph.D., Wolfgang M. Kuebler, M.D., Keith Tanswell, M.B., M.R.C.P.(U.K.), F.R.C.P.(C.), Rosetta Belcastro, B.Sc., Azhar Masood, M.D., Ph.D., Doreen Engelberts, A.H.T., Brian P. Kavanagh, M.B., M.R.C.P.(I.), F.R.C.P.(C.)



Citrullinated Histone co-localized with DNA

BUT … blockade of NET formation – no impact on injury in lung injury …

Anesthesiology 2015

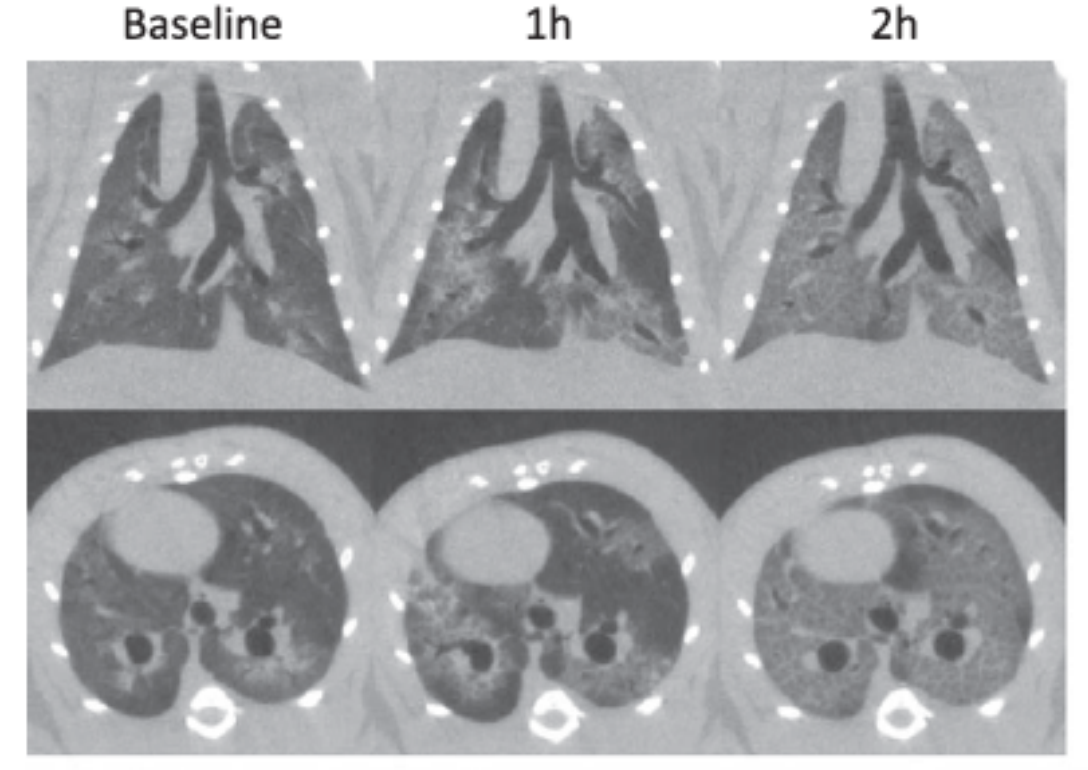
NETS occur in VILI but do not contribute to the injury

7. Local Factors

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 Kadlecek, 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.

Acid Aspiration



Anesthesiology 2016

Visualizing the Propagation of Acute Lung Injury

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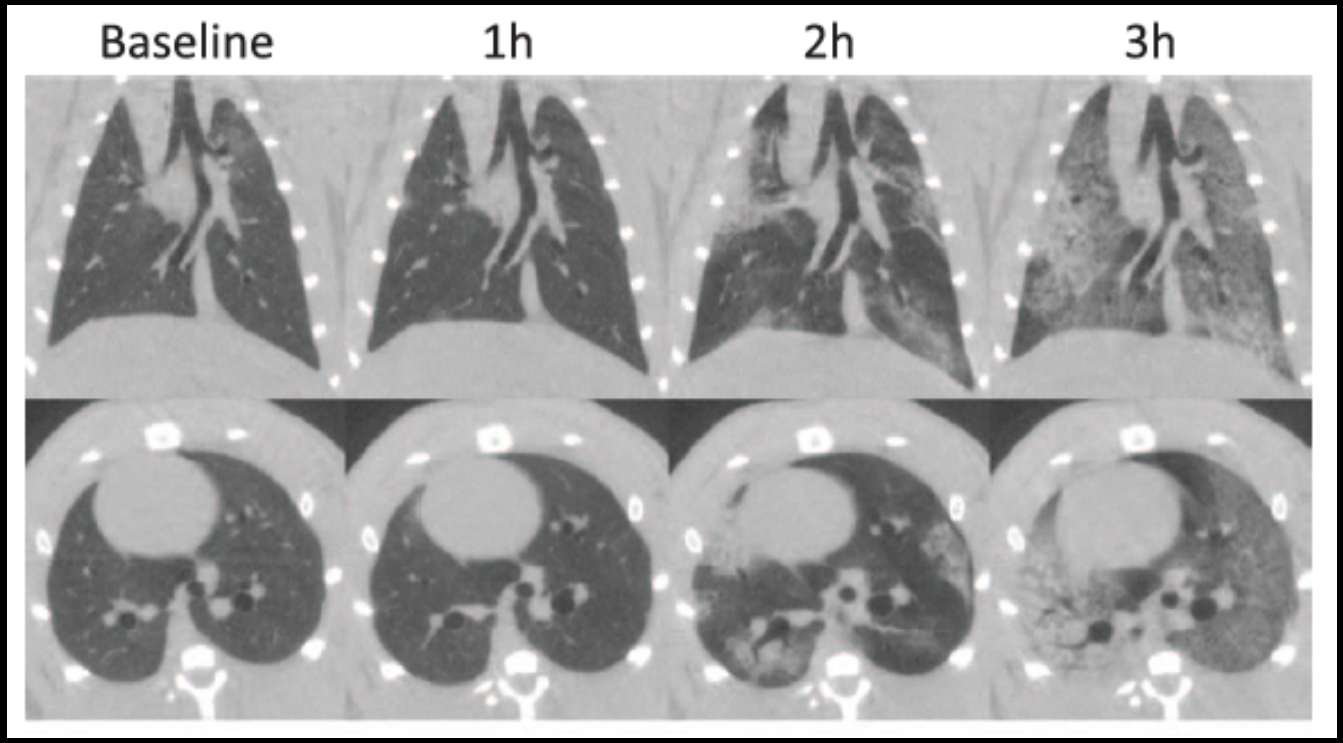
No Primary Injury



Anesthesiology 2016

Conclusions …

Prevent/Reverse Atelectasis

Inhibit/Augment Gene Products

Remove/Inhibit Circulating Mediators

Remain young (or old)

Block Sheddase

Role of NETs unclear

Local Factors

Treat the Lungs Gently, Understand the Mechanisms

Thank You

Brian.Kavanagh@utoronto.ca