Mediators and Lung Injury

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Conflicts of Interest

No financial conflict of interest with the subject matter of this talk
Experimental Pulmonary Edema due to Intermittent Positive Pressure Ventilation with High Inflation Pressures. Protection by Positive End-Expiratory Pressure

HERBERT H. WEBB and DONALD F. TIERNEY

Control 45/10 45/0

Am Rev Resp Dis 1974
Injurious Ventilatory Strategies Increase Cytokines and c-fos m-RNA Expression in an Isolated Rat Lung Model

Lorraine Tremblay,* Franco Valenza,‡ Sergio P. Ribeiro,‡ Jingfang Li,‡ and Arthur S. Slutsky‡

Effect of $V_T$, PEEP, & LPS

A: Saline

Tremblay et al, JCI 1997
What about perfusion?
Hyperventilation Induces Release of Cytokines from Perfused Mouse Lung

ALEXANDER NEPOMUK von BETTMANN, FRANK BRASCH, ROLF NÜSING, KATHRIN VOGT, HANS D. VOLK, KLAUS-MICHAEL MÜLLER, ALBRECHT WENDEL, and STEFAN UHLIG
Lung Injury

Circulating Mediators

Von Bethmann et al, AJRCCM 1998
More circulating mediators ...

... more lung injury
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 Mc Kerlie, Jaques Belik, Alison Fox-Robichaud, and Brian P. Kavanagh

Kornecki et al., Am J Respir Crit Care Med 2005
More ‘lung’ mediators ... ... more lung injury
Circulating mediators: Harmful to the lungs?
Lung-derived soluble mediators are pathogenic in ventilator-induced lung injury

Thomas Jaecklin, Doreen Engelberts, Gail O'Culakowski, Hugh O'Brodovich, Martin Post, and Brian P. Kavanagh
Don’t believe it ... ?
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
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Thomas Jaecklin,1 Doreen Engelberts,1 Gail Otulakowski,1 Hugh O’Brodovich,3 Martin Post,1 and Brian P. Kavanagh1,2
Characterization ... ?

... quite
All new concepts ... ?
RELEASE OF PROSTAGLANDIN $E_2$ AND UNIDENTIFIED FACTORS FROM VENTILATED LUNGS

BY ELLIOTT M. BERRY, JOHN F. EDMONDS, AND JOHN H. WYLLIE

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**Graphical Representation**

- **RSS**
- **RbA**
- **Combined antagonists**

**Critical Analysis**

- **2 $E_2$**
- **1 $E_2$**
- **4 $E_2$**
- **1 HT**
- **0.25 HT**
- **100 Ang II**
- **10 NAD**

**Legend**

- **20 ml x 32 per min. ng. per ml.**

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Br J Surg, 1971
42. Release of Prostaglandins caused by Distension of the Lungs: J. F. EDMONDS, E. BERRY, and J. H. WYLIE, Department of Surgery, University College Hospital Medical School, London.

During positive-pressure ventilation of the lungs the blood-pressure frequently falls, due to increased pressure in the thorax and consequent reduction of venous return. The following observations suggest that an additional factor may contribute to the hypotension.

1. When guinea-pig isolated lungs are perfused with Krebs's solution and are intermittently inflated, the effluent from them contains something which causes contraction of the rat stomach strip and the rat colon. The responsible agent is not oxygen, acetylcholine, histamine, or 5-hydroxytryptamine. When extracted, it behaves like an acid lipid and on chromatography contains components indistinguishable from prostaglandins E and F₂. The release of prostaglandins increases with increasing distension of the lungs.

The concentrations of prostaglandins in the effluent from the lungs was estimated to be 0.35 ng. per ml. of E₂ and 0.5 ng. per ml. of F₂.

2. A similar effect could be demonstrated in the anaesthetized dog; although the substance responsible was not formally identified, tissue reactions are consistent with its being a prostaglandin. The concentrations detected were of the order of 1 ng. per ml. (assayed as E₂) which is sufficient to cause a drop in the blood-pressure of an anaesthetized dog.

These results suggest that positive-pressure ventilation releases a prostaglandin-like substance which may contribute to circulatory collapse.
Summary

Mediators are produced by high $V_T$

- are present in the circulation
- contribute to (experimental) lung injury
- characterization … complicated
Thank you