predicting lung mechanics from dynamic surface tension evaluations of lung surfactants

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Workshop on Surfactant Driven Thin Film Flows to be held at the Fields Institute
Upon compression (exhalation) the lung surfactants produce a near zero surface tension that reduce the pressure difference between the smaller alveoli and the airways.

Laplace Pressure: \( \Delta P \sim \frac{\gamma}{R} \) (\( R \), radius of the alveolus)
The Engineering Approach

**In vivo**

- Surfactant chemistry and additives

**In vitro**

- Surfactant and lung mechanics

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**Humid air**

- Relative Area $A_r$
Composition of lung surfactants

• Phospholipids ~ 85-90%
  • Mainly phosphatidyl cholines (zwitterionic), and particularly dipalmitoyl phosphatidyl cholines (DPPC) to give solid-like properties.

• Phosphatidyl glycerols (anionic) that impart appropriate dynamic folding/unfolding properties to the surfactant film

• Neutral Lipids ~ 1-5% (cholesterol)

• Proteins ~ 5-10%
  • Surfactant Proteins A and D => anionic, hydrophilic
  • Surfactant Proteins B and C => cationic, hydrophobic
  • Surfactant Protein B is essential
Surfactant Evaluation => Compression isotherms

Wilhelmy Balance

Surface pressure = surface tension of the pure liquid ($\gamma_0$) - surface tension ($\gamma$)

Elasticity $\varepsilon = \frac{d\gamma}{d\ln(A)} = -\frac{dn}{d\ln(A)}$

Molecular area = $1$/surface concentration $= 1/\Gamma$
Evaluation of Surfactant Dynamics

Constrain Sessile Drop
Dynamic Evaluation => adsorption and relaxation effects

Adsorption and relaxation effects depend on:
- Compression dynamics
- Environment
- Surfactant composition
Compression Relaxation Model

\[
\frac{d\gamma}{dt} = \begin{cases} 
\frac{d\gamma_1}{dt} + \frac{d\gamma_2}{dt} & \text{if } \gamma \geq \gamma_{\text{min}} \\
0 & \text{if } \gamma \leq \gamma_{\text{min}}
\end{cases}
\]

where

\[
\frac{d\gamma_1}{dt} = \begin{cases} 
k_a (\gamma_{\text{eq}} - \gamma) & \text{if } \gamma \geq \gamma_{\text{eq}} \\
k_r (\gamma_{\text{eq}} - \gamma) & \text{if } \gamma \leq \gamma_{\text{eq}}
\end{cases}
\]

\[
\frac{d\gamma_2}{dt} = \begin{cases} 
\varepsilon_c \left( \frac{1}{A} \frac{dA}{dt} \right) & \text{if } \frac{dA}{dt} \leq 0 \\
\varepsilon_e \left( \frac{1}{A} \frac{dA}{dt} \right) & \text{if } \frac{dA}{dt} \geq 0
\end{cases}
\]

\(\gamma_{\text{eq}}\) Equilibrium surface tension

\(\gamma_{\text{min,c}}\) Minimum surface tension at collapse

\(k_a, k_r\) First order adsorption and relaxation constants

\(\varepsilon_c, \varepsilon_e\) Elasticity during compression and expansion
Compression Relaxation Model

Typical fit of CRM model

Parameters for specific scenarios

<table>
<thead>
<tr>
<th>Formulation</th>
<th>$\varepsilon_{c_f}$ mJ/m$^2$</th>
<th>$\varepsilon_{e_f}$ mJ/m$^2$</th>
<th>$k_{a_f}$ s$^{-1}$</th>
<th>$k_{r_f}$ s$^{-1}$</th>
<th>$\gamma_{\text{min}}$ mJ/m$^2$</th>
<th>$\gamma_{\text{eq}}$ mJ/m$^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLES</td>
<td>120</td>
<td>130</td>
<td>2.5</td>
<td>0.0</td>
<td>2</td>
<td>22</td>
</tr>
<tr>
<td>BLES-albumin</td>
<td>72</td>
<td>78</td>
<td>1.5</td>
<td>2.5</td>
<td>20</td>
<td>25</td>
</tr>
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</tr>
</tbody>
</table>
CRM - Pressure-Volume Model

Ventilator waveform:
\[ V = f(t) \]

CRM parameters:
\[ \gamma_{eq}, \gamma_{min,c}, k_a, k_r, \varepsilon_c, \varepsilon_e \]
\[ \gamma = f(A, t) \]

Prokop et al. (1999)
\[ A = f(V, \gamma) \]

Smith et al. (1986)
\[ P = P_{tissue}(V) + P_{capillary}(\gamma) \]
Tissue contribution to lung pressure

Dixon et al, 2009 (rats)
Smith and Stamenovic, 1987 (rabbits)
Simon et al, 2010 (mice)
CRM-PV algorithm

\[
(P)_t = 0.027\gamma_t + a/(b-V_t)
\]

\[
A_t = 0.0324V_t + 1.734 - 0.707\gamma_t^{0.366}
\]

Save \(\gamma_t, V_t, (P)_t, A_t\)

\(V_{t+\delta t}\) from ventilation function

\(\gamma_a = \gamma_t\)

\[
A_{t+\delta t} = 0.0324V_{t+\delta t} + 1.734 - 0.707\gamma_a^{0.366}
\]

\[
\left(\frac{dA}{dt}\right)_t = \frac{A_{t+\delta t} - A_t}{\delta t}
\]

If \((dA/dt)_t < 0, \varepsilon = \varepsilon_c\), else \(\varepsilon = \varepsilon_e\)

If \(\gamma_a < \gamma_{eq}\), \(k=k_c\), else \(k=k_a\)

\[
\left(\frac{d\gamma}{dt}\right)_t = \frac{\varepsilon}{A_t} \left(\frac{dA}{dt}\right)_t + k(\gamma_{eq} - \gamma_a)
\]

\(\gamma_n = \gamma_t + (d\gamma/dt)_t \delta t\)

If \(\gamma_n < \gamma_{min}\), \(\gamma_{t+\delta t} = \gamma_{min}\), else \(\gamma_{t+\delta t} = \gamma_n\)

\(\gamma_{t+\delta t} = \gamma_a?\)

Yes

\(t = t+\delta t\)

No

\(t > t_{max}\) ?

Yes

End
CRM – PV – rabbit model

- CRM-PV prediction – BLES
- Bachofen et al. (1987)

Graphs showing:
- % Total lung capacity (TLC) vs. Surface tension, mJ/m
- % Total lung capacity (TLC) vs. Pressure, cm H2O
- Lung area, m

Graphs illustrate the relationship between lung capacity and various parameters.
CRM – PV –mice model

Experiments of Allen and Bates

CRM-PV

BLES

CRM-PV

BLES - ALBUMIN

CONTROL

HCl injury model of ARDS

% Total lung capacity (TLC)

Pressure, cm H2O

Volume, ml

Pressure, cm H2O
CRM – PV, dynamic properties

CRM-PV prediction of lung elastance (ΔP/ ΔV) – left – and experimental values –right - using variable ventilation

*** low minimum surface tension is not always important ***

Fast surfactant adsorption is essential
Conclusions

1 – *In vitro* – *in vivo* correlations are closer to reality => integrated approach to design surfactant therapies

2 – Much to be learned of the physics of surfactant membranes at the molecular scale

3 – A combination of strategies: surfactant additives, method of ventilation may be used in alternative therapies

4 – Need to introduce flow-driven pressure drop

5 – Need to incorporate surfactant spreading
Acknowledgements

• Canada Institute for Health Research (CIHR)
• BLES Biochemicals (London, Ontario)
Surfactant membrane conformations
Compression Relaxation Model

% Area reduction (compression)

Elasticity slightly improves with surfactant concentration
Compression Relaxation Model

Relaxation constant is not a function of surfactant concentration
Compression Relaxation Model

Adsorption constant tends to increase with surfactant concentration

BLES 2 mg/ml

BLES 27 mg/ml

% Area reduction (compression)
Cationic Surfactant Additives

Reasoning:

Cationic additives can be used to induce flocculation and larger, more active, surfactant aggregates.

SP-B, a cationic protein, is essential to life.

The anionic headgroup of phosphatidyl glycerols seems to easily hydrate, weakening the surfactant film.
Effect of Chitosan on BLES

Addition of chitosan, up to a certain ratio, induce larger aggregates to form, also improving the surface activity.
Effect of Chitosan on BLES

Cationic surfactant additives can improve the elasticity of exogenous surfactant and reduce the relaxation constant.
Cationic additives may be the answer to ARDS

550 μl/ml serum simulates the high protein content in the lungs of ARDS patients. Even a high exogenous surfactant concentration ~ 27 mg/ml BLES would not work
Effect of cationic peptides

2 mg/ml BLES + additive

- BLES only
- 0.20 mg/ml Polysine 50kDa
- 0.10 mg/ml Polymyxin B
- Complete lung surfactant

Physiologically active formulations

Polymyxin B