Intraoperative ventilation strategy during cardiopulmonary bypass attenuates the release of matrix metalloproteinases and improves oxygenation
Open heart surgery with CPB
Coronary artery bypass graft
Coronary artery bypass graft

- Low mortality (2.63%)
- 10-25% mild respiratory dysfunction
- 2-5% severe respiratory dysfunction
  —> High mortality

Elevation of both proinflammatory and anti-inflammatory mediators —> multiple organ dysfunction

Matrix metalloproteinases
Matrix metalloproteinases

- Zinc- and calcium-dependent endopeptidases
  —> metzincin superfamily
- produced in various types of cells, including
  - inflammatory
  - stromal
  - epithelial & endothelial cells
- MMP-2,19,28 and several MT-MMPs —> homeostasis
- Most induced by
  - infection
  - tissue injury (CABG)
Structure

Typical MMPs
- **Collagenases**
  - MMP-1, -8, and -13
- **Stromelysins**
  - MMP-3 and -10
- **Others**
  - MMP-12, -19, and -20

Gelatinases
- MMP-2 and -9

Matrilysins
- MMP-7 and -26

Furin-activatable MMPs
- **Secreted**
  - MMP-11, -21, and -28
- **Type I TM**
  - MMP-14, -15, -16, and -24
- **Type II TM**
  - MMP-23
- **GPI-anchored**
  - MMP-17 and -25

Signal peptide
- Prodomain
- Linker
- Proprotein convertase recognition sequence
- Catalytic domain
- Fibronectin type II motif
- Hinge
- Hemopexin domain
- Transmembrane type I domain
- Cytoplasmic domain
- Transmembrane type II domain
- GPI anchoring domain
- Cysteine-rich domain
- Immunoglobulin-like domain

"Matrix Metalloproteinases in Non-Neoplastic Disorders"
A. Tokito and M. Jougasaki
a Path-clearing through the ECM
Mesenchymal cell

b ECM proteolysis generates signalling molecules

b ECM proteolysis generates signalling molecules

MMP

Proliferation
Cell death
Cell motility
Proliferation
Cell death
Cell motility
Differentiation

MMP

Cell death
Cell motility
Proliferation

Adipocyte

MMP

Junctionally coupled epithelial cells

Basement membrane

Degradation of intercellular junctions

Degradation of basement membrane

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Functions

- Degradation
- Homeostatic functions
  - tissue remodeling
  - wound healing
  - immunity
- Shedding of cell surface receptors
- Mediate the bioactive state and local delivery of signaling molecules
Activation vs Inhibition

Activation

—> disruption of cystein-switch

- Cytokines
  - TNF-α
  - IL-6, IL-8, IL-10

- Autolysse

- Proteinases
  - Plasmin
  - Trypsin
  - Furin
  - other MMPs

- Oxydation by reactive oxygen species
Activation vs Inhibition

Inhibition

• General protease inhibitors
  - α₂-macroglobulin
  - Tissue inhibitors (TIMPs)

• Catalytic activity controlled by
  - Gene expression
  - Transcription
  - Translation
  - Zymogen activation
  - Compartmentalization
  - RNA stability
  - TIMPs
Respiratory Dysfunction

• **Pulmonary Emphysema** (COPD)
  - alveolar macrophages (MMP-1,-9,-12)

• **Interstitial Pulmonary Fibrosis**
  - cleavage of basement membrane (acute lung injury)
  - collagen accumulation (MMP-1,-2,-3,-7,-9,-14)

• **Asthma**
  - chronic inflammation (MMP-2,-8,-9)

• **Tuberculosis**
  - destruction of the lung ECM for spreading (MMP-1,-2,-8,-9)
Lipocain 2

• Build a complex with MMP-9 —> stabilize

• Associated with higher incidence of
  - pulmonary failure
  - longer ICU stay
  - hospital stay


„Early blood biomarkers predict organ injury and resource utilization following complex cardiac surgery“
Therapeutic Implications

• Synthetic inhibitors
• Certain effects in experimental models
• **All clinical trials failed**
  - inadequate end points
  - metabolic instability
  - low oral availability
  - poor inhibitory specificity
  - adverse side effects
• Complex effects
Mechanical ventilation as solution to prevent systemic immune response
Intraoperative ventilation strategy during cardiopulmonary bypass attenuates the release of matrix metalloproteinases and improves oxygenation
Material and methods
Table 1 – Patient characteristics.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>VG (n = 15)</th>
<th>NVG (n = 15)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male/female)</td>
<td>12/3</td>
<td>13/2</td>
<td>0.62</td>
</tr>
<tr>
<td>Age</td>
<td>65 (46–80)</td>
<td>66 (47–76)</td>
<td>0.86</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.0 ± 0.7</td>
<td>28.9 ± 0.9</td>
<td>0.65</td>
</tr>
<tr>
<td>COPD</td>
<td>6</td>
<td>6</td>
<td>1.0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>14</td>
<td>10</td>
<td>0.07</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>50 ± 5</td>
<td>53 ± 9</td>
<td>0.17</td>
</tr>
<tr>
<td>EuroSCORE</td>
<td>5 (2–8)</td>
<td>4 (1–12)</td>
<td>0.42</td>
</tr>
<tr>
<td>Indication (elective/urgent)</td>
<td>11/4</td>
<td>9/6</td>
<td>0.44</td>
</tr>
<tr>
<td>Creatinine (µmol/L)</td>
<td>84 (67–113)</td>
<td>75 (60–1132)</td>
<td>0.384</td>
</tr>
<tr>
<td>Instable angina pectoris</td>
<td>0</td>
<td>1</td>
<td>0.31</td>
</tr>
<tr>
<td>NYHA class III</td>
<td>15</td>
<td>15</td>
<td>1.0</td>
</tr>
<tr>
<td>Preoperative stroke</td>
<td>2</td>
<td>1</td>
<td>0.53</td>
</tr>
<tr>
<td>Status post-AMI</td>
<td>7</td>
<td>8</td>
<td>0.72</td>
</tr>
<tr>
<td>Preoperative PCI</td>
<td>5</td>
<td>4</td>
<td>0.69</td>
</tr>
</tbody>
</table>

AMI = acute myocardial infarction; BMI = body mass index; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; NYHA = New York Heart Association; PCI = percutaneous coronary intervention.

Data are given as mean ± standard deviation, median (interquartile range), or absolute numbers, respectively.
### Results

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>VG (n = 15)</th>
<th>NVG (n = 15)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of grafts</td>
<td>4 (2–5)</td>
<td>4 (2–5)</td>
<td>0.72</td>
</tr>
<tr>
<td>Aortic cross-clamp time (min)</td>
<td>55 ± 11</td>
<td>58 ± 17</td>
<td>0.24</td>
</tr>
<tr>
<td>CPB duration (min)</td>
<td>95 ± 19</td>
<td>100 ± 25</td>
<td>0.66</td>
</tr>
<tr>
<td>ICU stay (h)</td>
<td>22 (17–45)</td>
<td>50 (17–172)</td>
<td>0.82</td>
</tr>
<tr>
<td>Hospital stay (d)</td>
<td>6 (6–12)</td>
<td>7 (6–19)</td>
<td>0.31</td>
</tr>
<tr>
<td>Ventilation support (h)</td>
<td>9 (4.5–20)</td>
<td>8 (4.5–85)</td>
<td>0.70</td>
</tr>
<tr>
<td>Blood loss (mL)</td>
<td>700 ± 400</td>
<td>600 ± 500</td>
<td>0.25</td>
</tr>
<tr>
<td>Autotransfusion (mL)</td>
<td>350 ± 330</td>
<td>400 ± 370</td>
<td>0.53</td>
</tr>
<tr>
<td>Units of RBC transfused</td>
<td>1 (0–5)</td>
<td>2 (0–6)</td>
<td>0.59</td>
</tr>
<tr>
<td>Hb preoperative (g/dL)</td>
<td>13.6 ± 1.5</td>
<td>13.6 ± 1.6</td>
<td>0.73</td>
</tr>
<tr>
<td>Hb at the end of surgery (g/dL)</td>
<td>9.8 ± 0.9</td>
<td>10.1 ± 1.2</td>
<td>0.37</td>
</tr>
<tr>
<td>Hb POD-1 (g/dL)</td>
<td>10.9 ± 0.9</td>
<td>10.7 ± 1.2</td>
<td>0.89</td>
</tr>
<tr>
<td>CRP POD-1 (mg/dL)</td>
<td>105 ± 68</td>
<td>142 ± 81</td>
<td>0.19</td>
</tr>
<tr>
<td>CRP POD-5 (mg/dL)</td>
<td>45 ± 18.5</td>
<td>68 ± 44</td>
<td>0.08</td>
</tr>
<tr>
<td>WBC POD-1 (G/L)</td>
<td>11 ± 4</td>
<td>13 ± 4</td>
<td>0.048</td>
</tr>
<tr>
<td>WBC POD-5 (G/L)</td>
<td>7 ± 2</td>
<td>8 ± 2</td>
<td>0.16</td>
</tr>
<tr>
<td>Reoperation because of bleeding</td>
<td>0</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>Atrial fibrillation postoperative</td>
<td>4</td>
<td>2</td>
<td>0.32</td>
</tr>
<tr>
<td>Perioperative AMI</td>
<td>1</td>
<td>0</td>
<td>0.31</td>
</tr>
<tr>
<td>Pericardial tamponade</td>
<td>0</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>28-d mortality</td>
<td>0</td>
<td>0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

AMI = acute myocardial infarction; CRP = C-reactive protein; Hb = hemoglobin; PCI = percutaneous coronary intervention; RBC = red blood cells; WBC = white blood count.

Data are given as mean ± standard deviation, median (interquartile range), or absolute numbers, respectively.
<table>
<thead>
<tr>
<th>Oxygenation indices</th>
<th>T0</th>
<th>T1</th>
<th>T2</th>
<th>P value T1 versus T2</th>
<th>T3</th>
<th>P value T1 versus T3</th>
<th>T4</th>
<th>P value T2 versus T4</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO2/FiO2 (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NVG</td>
<td>385 ± 37</td>
<td>416 ± 140</td>
<td>291 ± 139</td>
<td>0.0013</td>
<td>265 ± 120</td>
<td>0.0072</td>
<td>253 ± 102</td>
<td>0.0002</td>
</tr>
<tr>
<td>VG</td>
<td>404 ± 50</td>
<td>475 ± 135</td>
<td>392 ± 121</td>
<td>0.011</td>
<td>362 ± 111</td>
<td>0.0019</td>
<td>335 ± 97</td>
<td>0.0081</td>
</tr>
<tr>
<td>P value between groups</td>
<td>0.24</td>
<td>0.25</td>
<td>0.045</td>
<td>—</td>
<td>0.029</td>
<td>—</td>
<td>0.0387</td>
<td>—</td>
</tr>
<tr>
<td>PEEP (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NVG</td>
<td>4</td>
<td>4</td>
<td>1.0</td>
<td>4 ± 1.8</td>
<td>0.10</td>
<td>4 ± 1.8</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>VG</td>
<td>4</td>
<td>4</td>
<td>1.0</td>
<td>4 ± 0.6</td>
<td>0.10</td>
<td>4 ± 0.6</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>P value between groups</td>
<td>1.00</td>
<td>1.00</td>
<td>—</td>
<td>0.25</td>
<td>—</td>
<td>0.32</td>
<td>—</td>
<td></td>
</tr>
</tbody>
</table>

PaO2/FiO2 = Horovitz-Index; T0 = before induction of anesthesia; T1 = after the induction of anesthesia; T2 = at the end of surgery; T3 = immediately after admission to the ICU; T4 = 6 h after surgery.

Data are given as mean ± standard deviation.
Results
Results

+ Attenuation of systemic MMP-release and TIMP-1
+ Also decrease of LCN2!
+ Significantly higher PaO$_2$/FiO$_2$ ratio (Horovitz index)
+ Reduced alveolar-arterial oxygen difference (AaDO$_2$)
+ Decreased shunt fraction
+ Decrease of IL-10, sST2 and IL-6 concentrations
How does ventilation during CPB modulate the MMP-TIMP-LCN-2-axis?
How does ventilation during CPB modulate the MMP-TIMP-LCN-2-axis?

1. Reduction of pulmonary I/R injury
2. Influence on formation of pulmonary atelectasis and consecutive pulmonary neutrophil sequestration and activation
3. Activation of the complement system by mechanical shear stress
Discussion
Discussion

- Few clinical variables
- Small sample size
- No influence on
  - length of ventilatory support
  - duration of ICU
- Only venous serum samples
- Patients only with obstructive lung disease
- No lung function tests before operation

=> further research on high risk groups
Further discussion

• Calvin S.H. Ng, MD et al.
  *Ventilation During Cardiopulmonary Bypass: Impact on Cytokine Response and Cardiopulmonary Function (2003)*
  —> No difference in MMP-9 plasma concentration
  —> higher TIMP-1 levels in VG

• Jan-Uwe Schreiber, MD, PhD et al.
  *The Effect of Different Lung-Protective Strategies in Patients During Cardiopulmonary Bypass: A Meta-Analysis and Semiquantitative Review of Randomized Trials*
  —> "weak evidence"
  —> "positive effects (...) short lived with questionable impact"
  —> Impact on ICU and Intubation times only reported by few studies
    - Minkovic (2007)
    - John (2008)

• Hergrueter AH, Nguyen K, Owen CA.
  *Matrix metalloproteinases: all the RAGE in the acute respiratory distress syndrome*
  —> MMP-8 important for pathogenesis of acute lung injury

• Kim JH, Suk MH, Yoon DW, et al.
  *Inhibition of matrix metalloproteinase-9 prevents neutrophilic inflammation in ventilator-induced lung injury*
  —> Inhibition of MMP-9 attenuated ventilator induced lung injury
  (animal model)
Thank you for your attention