

Intraoperative ventilation strategy during cardiopulmonary bypass attenuates the release of matrix metalloproteinases and improves oxygenation

Open heart surgery with CPB

Coronary artery bypass graft

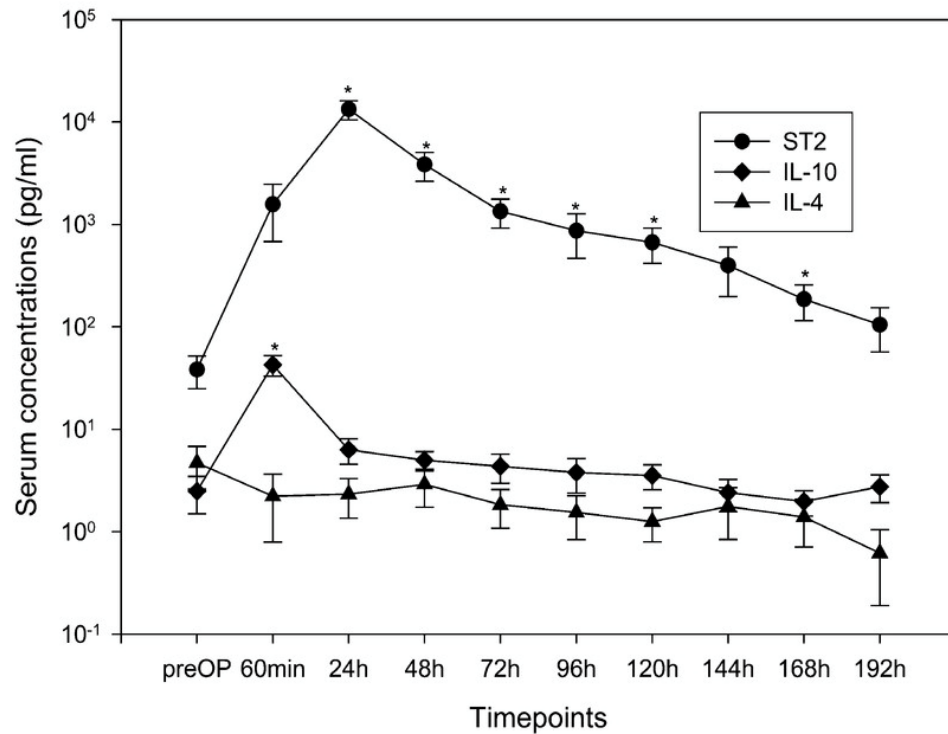


Coronary artery bypass graft

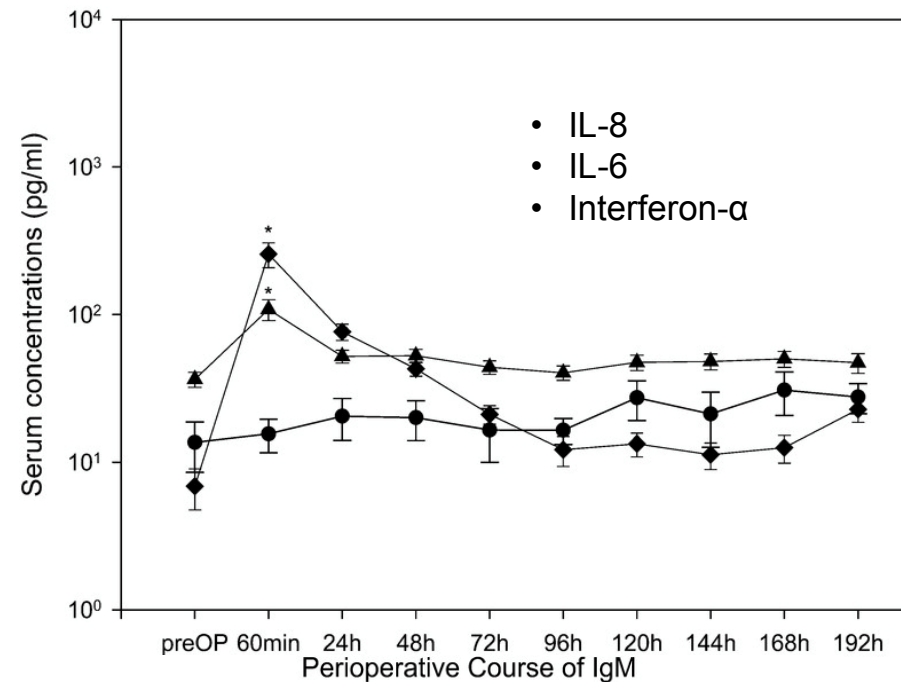
- Low mortality (2,63%)
- 10-25% mild respiratory dysfunction
- 2-5% severe respiratory dysfunction
—> High mortality

„Current status and outcomes of coronary revascularization 1999 to 2002: 148,396 surgical and percutaneous procedures“ - Michael J.MackMD, Edmund R.BeckerPhD

TH2 Cytokines

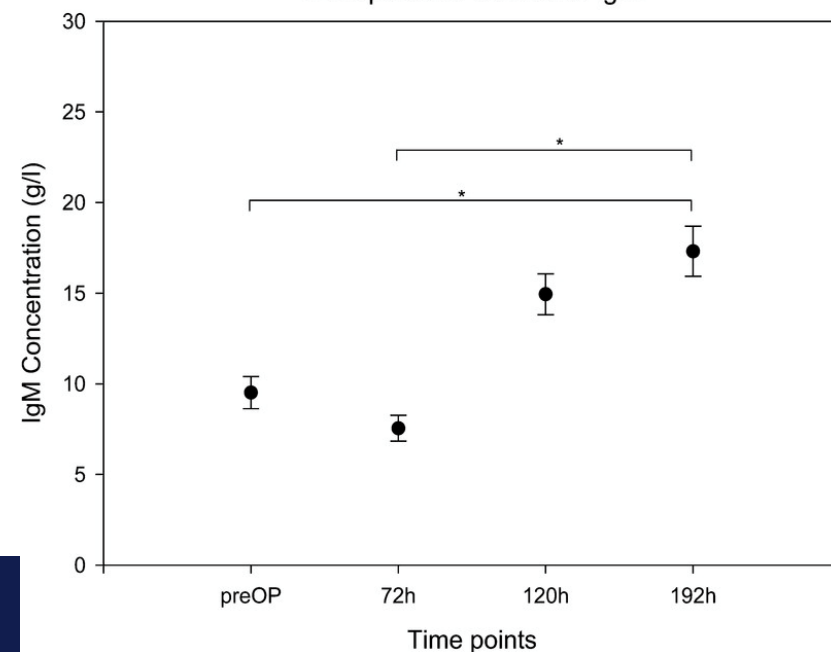


TH1 Cytokines



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

Secretion of Soluble ST2 – Possible Explanation for Systemic Immunosuppression after Heart Surgery - T. Szerafin₁ [], T. Niederpold₂ [*], A. Mangold₂ [*], K. Hoetzenecker₂, S. Hacker₂, G. Roth₃, M. Lichtenauer₂, M. Dworschak₃, E. Wolner₂, H. J. Ankersmit*



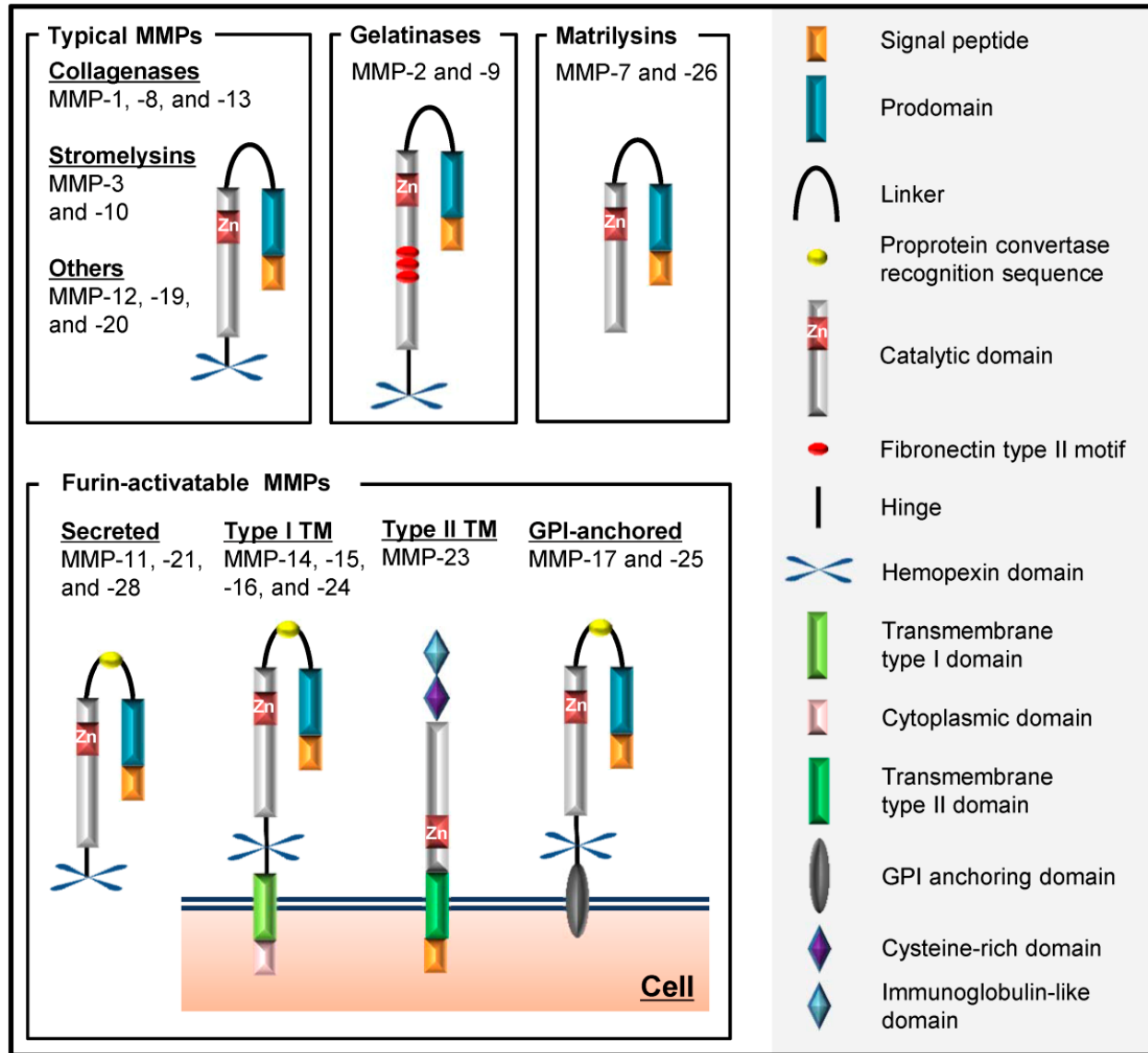
Matrix metalloproteinases



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)**

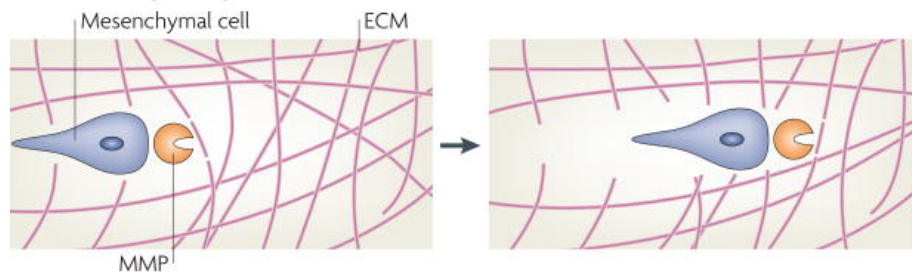
Structure



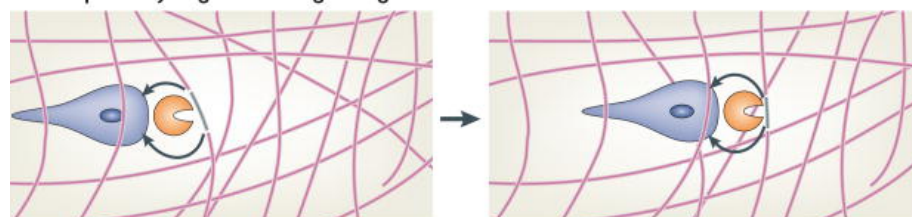
„Matrix Metalloproteinases in Non-Neoplastic Disorders“

A. Tokito and M. Jougasaki

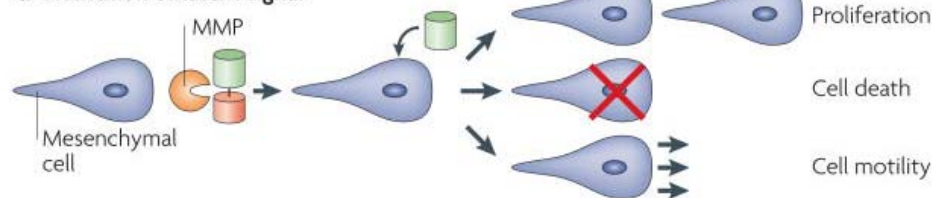
a Path-clearing through the ECM



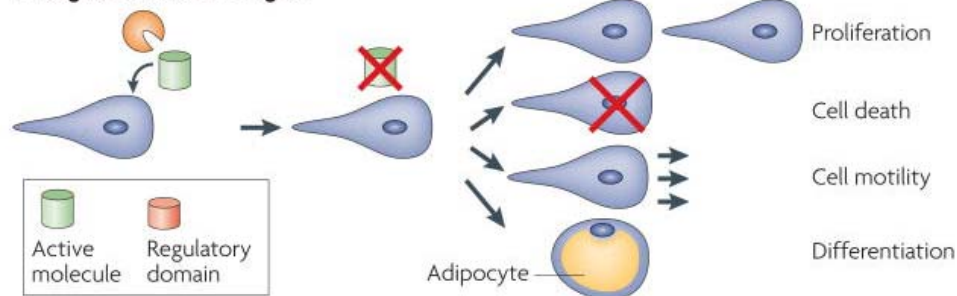
b ECM proteolysis generates signalling molecules



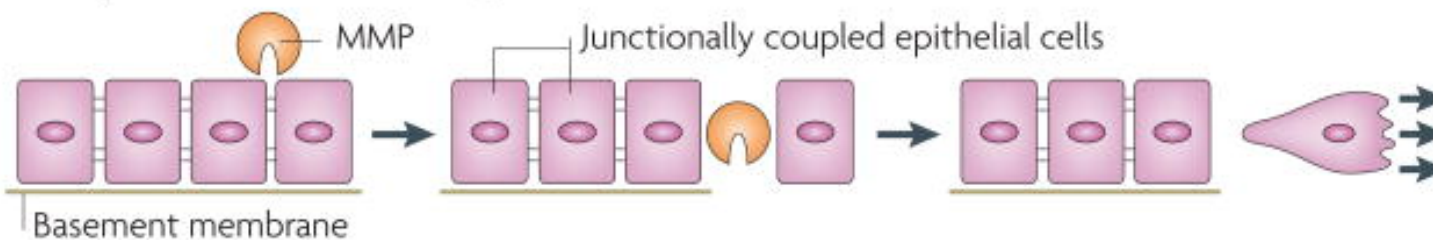
d Activation of latent signal



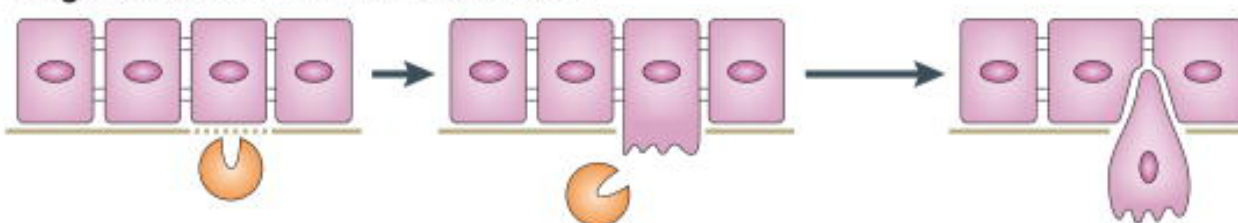
e Regulation of active signal



c Degradation of intercellular junctions



Degradation of basement membrane



Functions

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

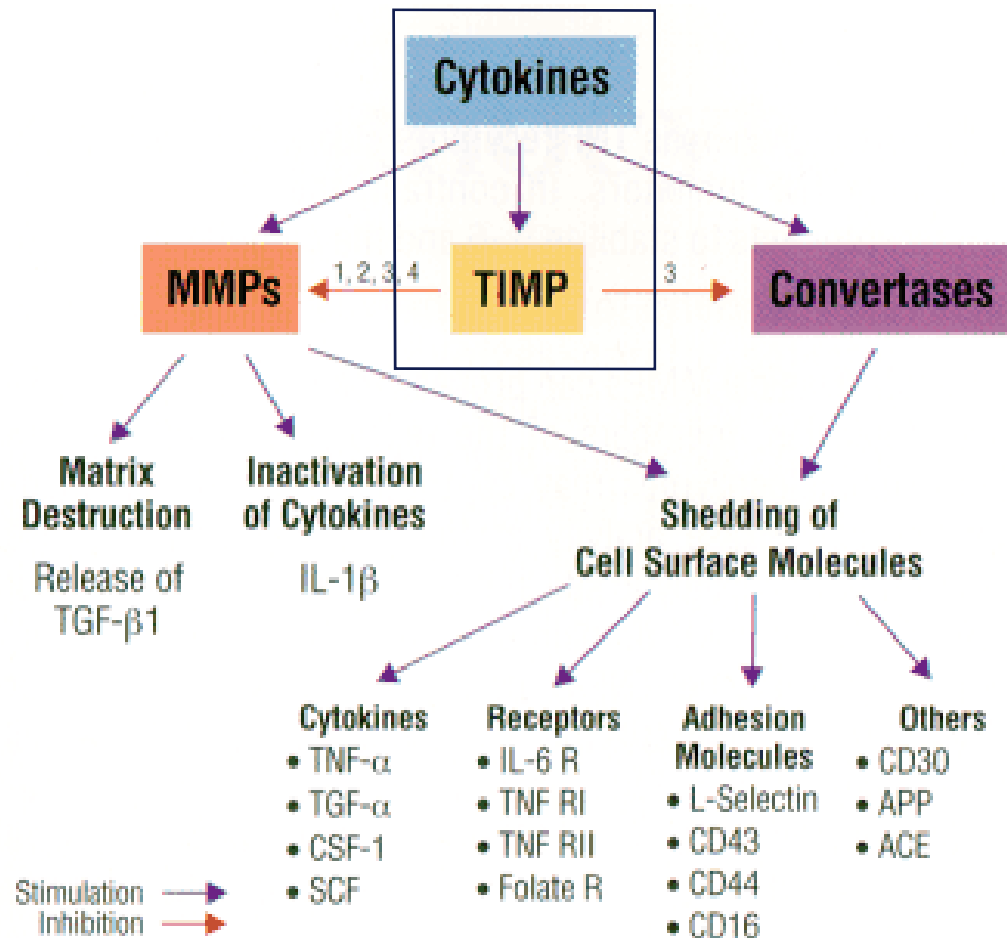


Figure 2. The MMP/Cytokine Connection

Activation vs Inhibition

Activation

—> disruption of cystein-switch

- Cytokines
 - TNF- α
 - IL-6, IL-8, IL-10
- Autolyse
- Proteinases
 - Plasmin
 - Trypsin
 - Furin
 - other MMPs
- Oxydation by reactive oxygen species

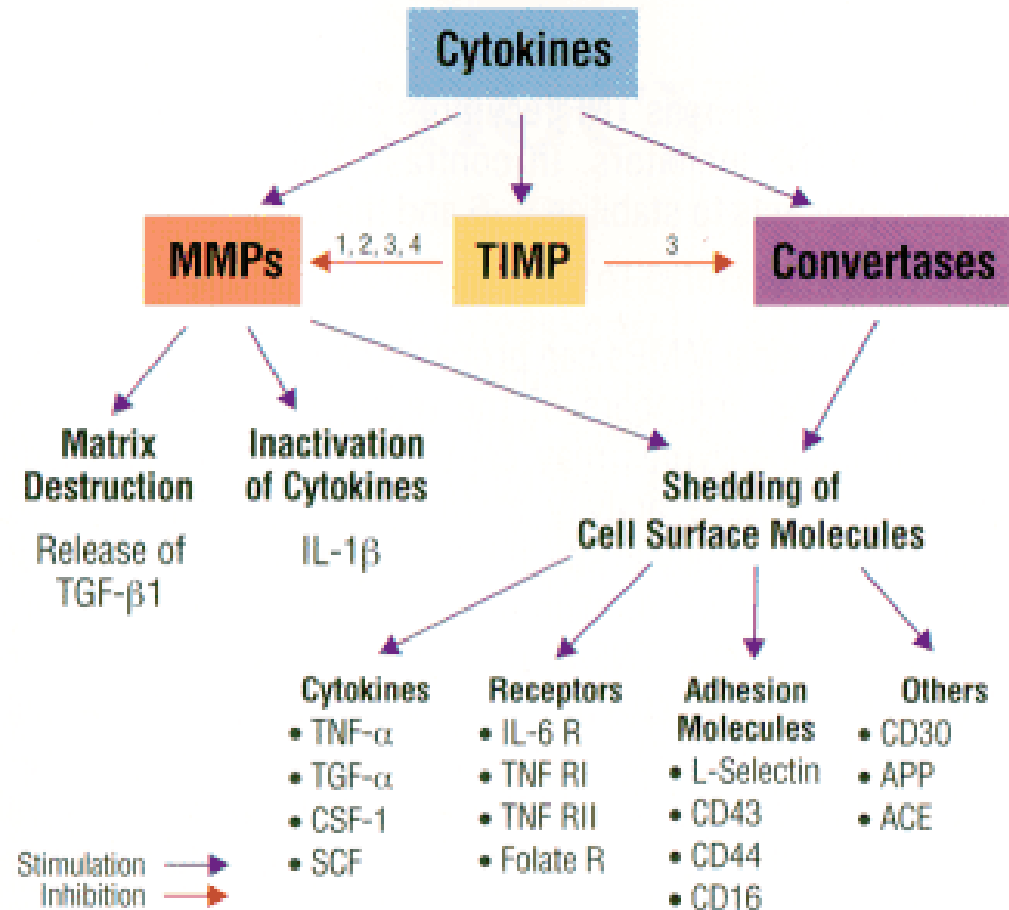
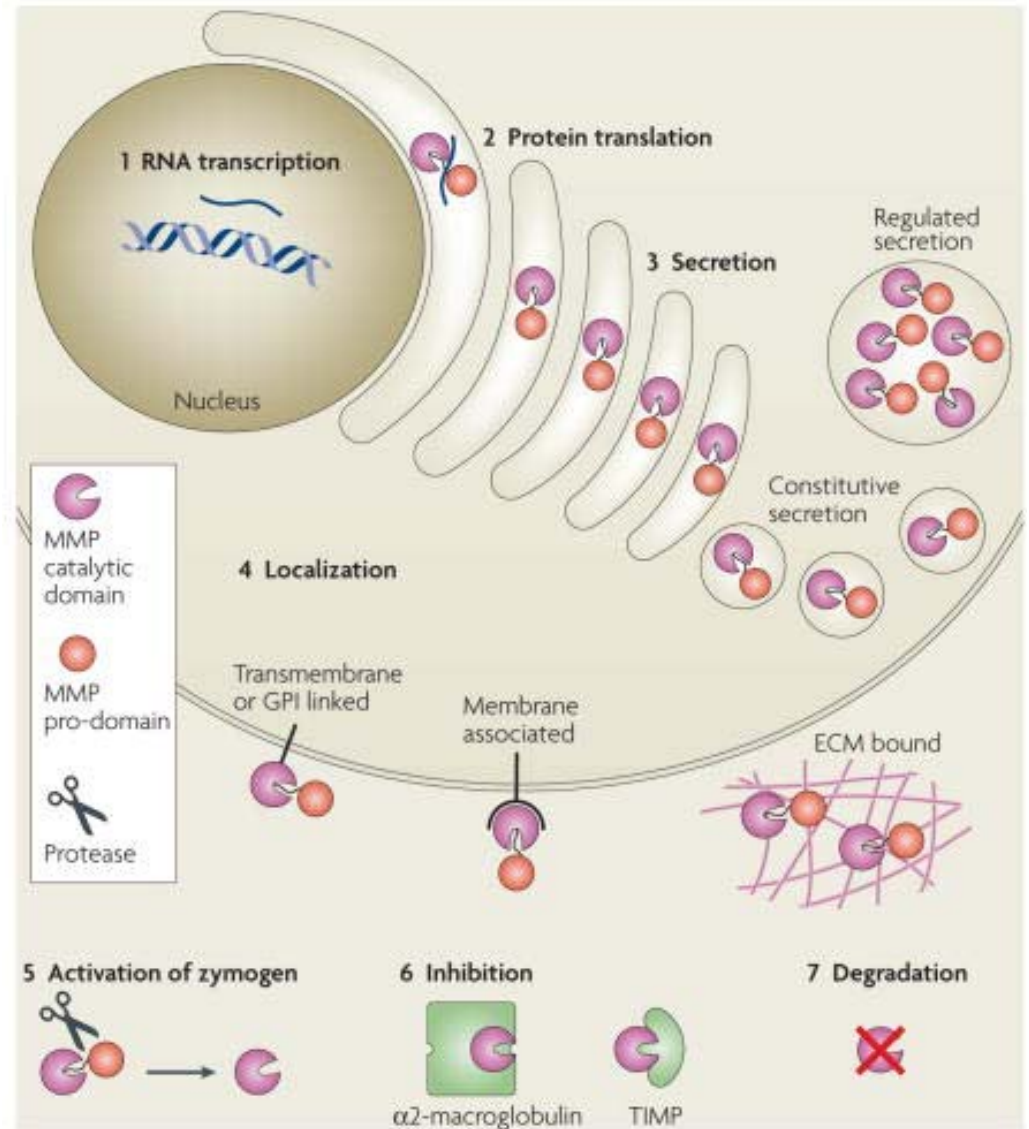


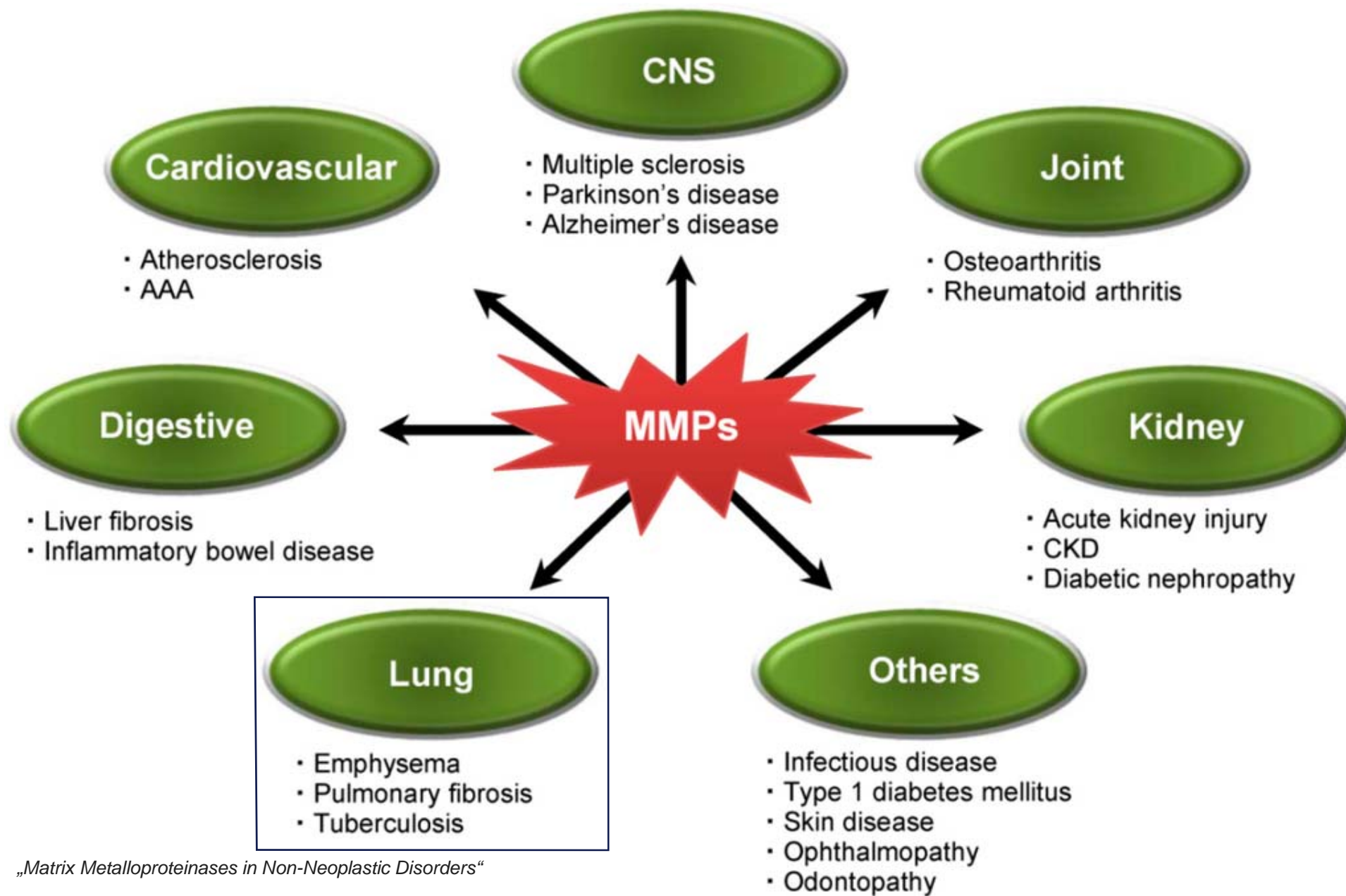
Figure 2. The MMP/Cytokine Connection

Activation vs Inhibition

Inhibition

- General protease inhibitors
 - α_2 -macroglobulin
 - Tissue inhibitors (**TIMPs**)
- Catalytic activity controlled by
 - Genexpression
 - Transcription
 - Translation
 - Zymogenactivation
 - Compartmentalization
 - RNA stability
 - **TIMPs**





„Matrix Metalloproteinases in Non-Neoplastic Disorders“

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

Kim T, Arnaoutakis GJ, Bihorac A, et al.

„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.

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

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 2 – Clinical characteristics of subjects.

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

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.

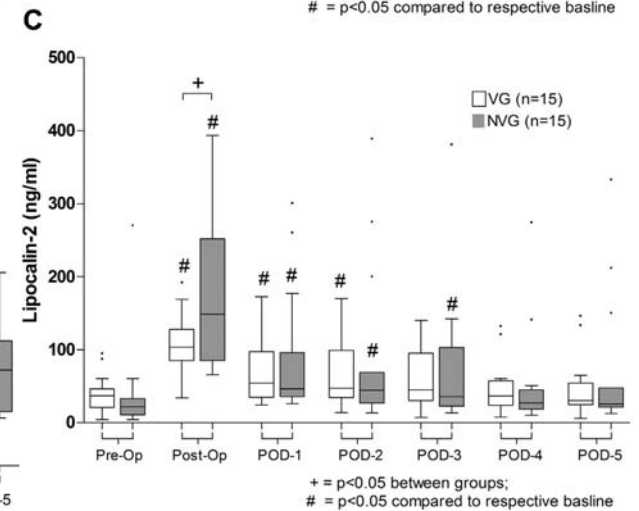
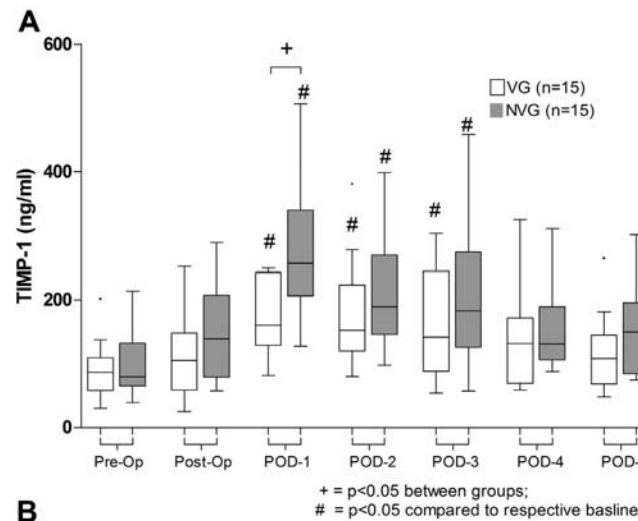
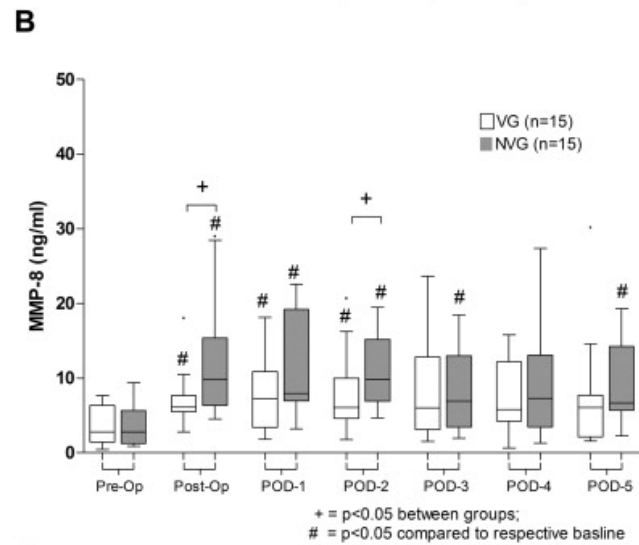
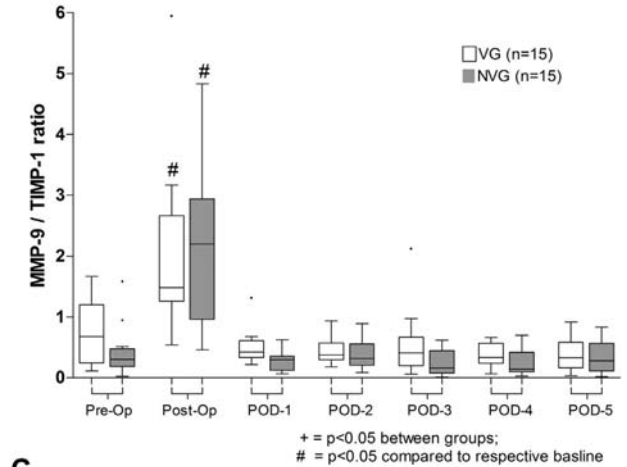
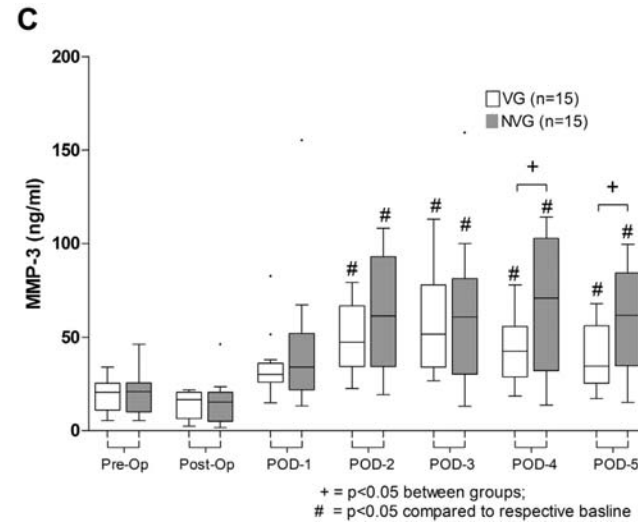
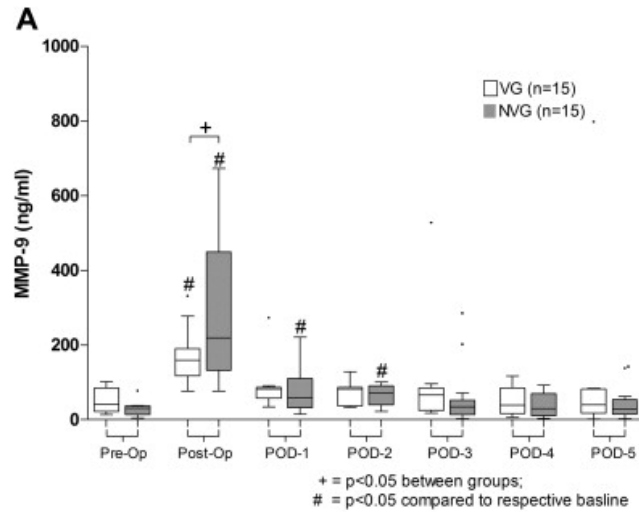
Table 3 – Comparison of oxygenation indices between groups.

Oxygenation indices	T0	T1	T2	P value T1 versus T2	T3	P value T1 versus T3	T4	P value T2 versus T4
PaO ₂ /FiO ₂ (mm Hg)								
NVG	385 ± 37	416 ± 140	291 ± 139	0.0013	265 ± 120	0.0072	253 ± 102	0.0002
VG	404 ± 50	475 ± 135	392 ± 121	0.011	362 ± 111	0.0019	335 ± 97	0.0081
P value between groups	0.24	0.25	0.045	—	0.029	—	0.0387	—
PEEP (mm Hg)								
NVG		4	4	1.0	4 ± 1.8	0.10	4 ± 1.8	0.10
VG		4	4	1.0	4 ± 0.6	0.10	4 ± 0.6	0.06
P value between groups		1.00	1.00	—	0.25	—	0.32	—

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 PaO₂/FiO₂ ratio (Horovitz index)**
- + **Reduced alveolar-arterial oxygen difference (AaDO₂)**
- + **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
 - Ayad (2003)
 - Minkovic (2007)
 - John (2008)
- Hergueter 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**

