



9th International Congress *and* Scientific Seminar 2009 – Bangladesh Society of Medicine, Dhaka, Bangladesh



Pulmonary Coagulopathy

Pulmonary Coagulopathy as a New Therapeutic Target



Marcus Schultz



Academisch Medisch Centrum

ST. MICHAEL'S HOSPITAL



Remember.
It all starts
with caring.

Give to's Urban Area Call





CHATTAGRAM
MEDICAL
HOSPITAL

চট্টগ্রাম
মেডিকেল কলেজ হাসপাতাল

স্বাস্থ্য সেবা

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OUT

প্রবেশ

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OUT

CSBCS
CSBCS



Disclosure

- Marcus Schultz has received speaker fees from Ely Lilly and Co, Leo Pharma, Sanofi–Aventis, Hamilton Medical and Maquet
- Marcus Schultz participated in studies sponsored by Leo Pharma, Novartis, and Hamilton Medical
- Marcus Schultz is sponsored by grants from the Dutch Government (ZonMW) and the ESICM
- Marcus Schultz performs an Organon–sponsored trial
- Marcus Schultz is, or has been an advisor of Novartis and Leo Pharma



Frame Work of this Presentation

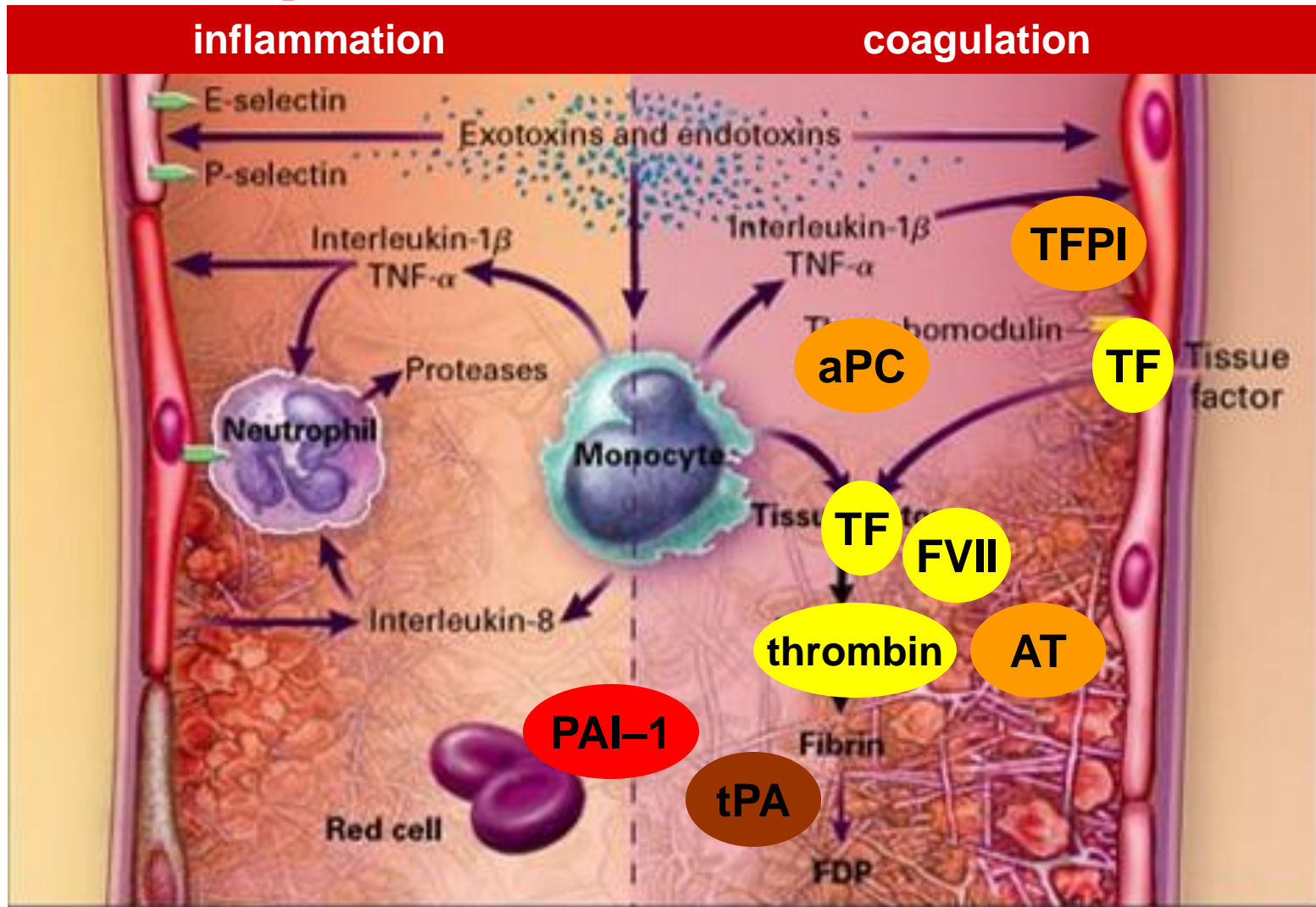
- Systemic coagulation with systemic inflammation
- Local coagulation with pulmonary inflammation
- Rational for anticoagulant strategies for lung injury
- Presently performed *preclinical* studies
- Presently performed *clinical* studies
- Conclusions



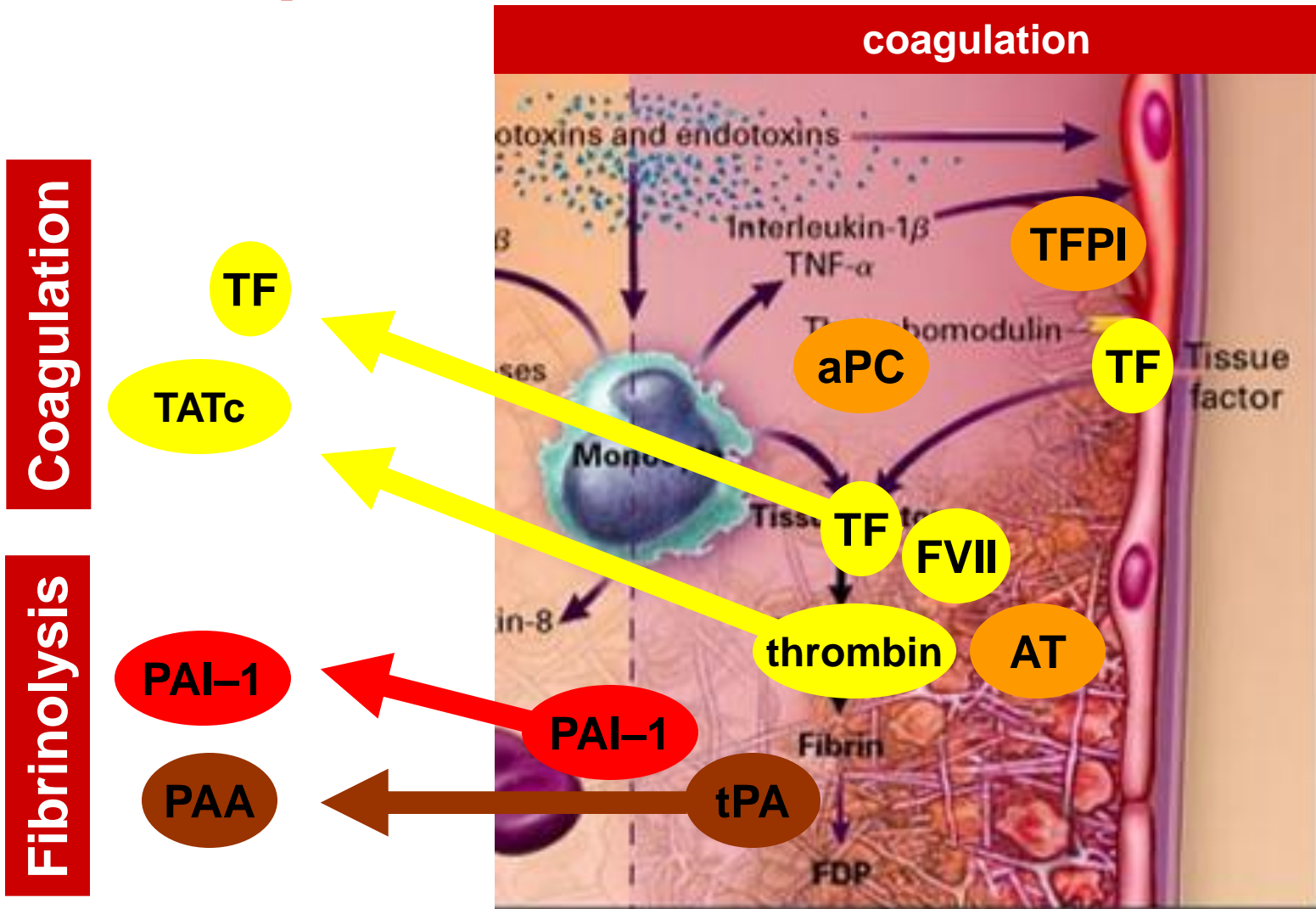
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Coagulopathy with SIRS, Sepsis and Septic Shock

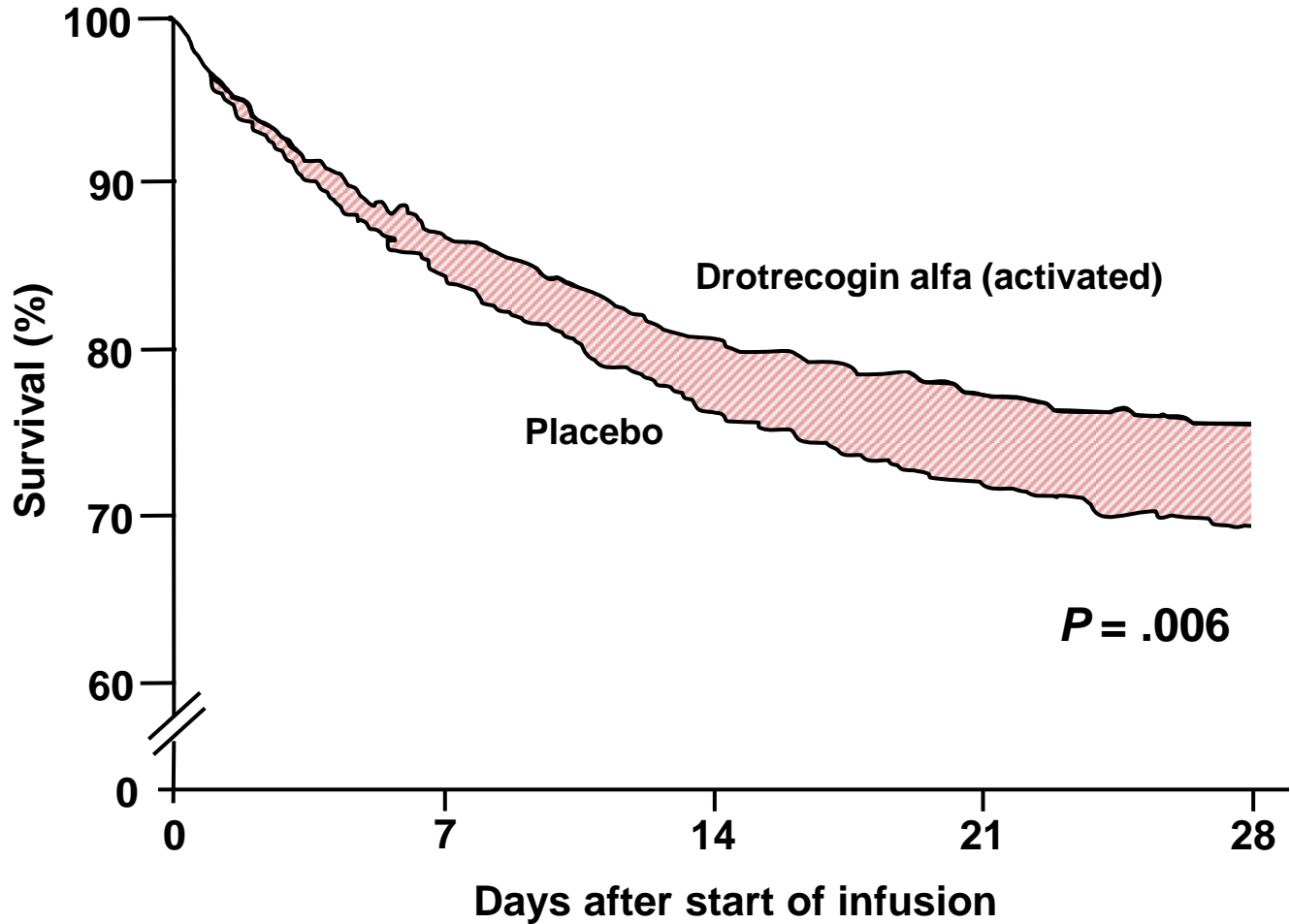


Coagulopathy with SIRS, Sepsis and Septic Shock





Anticoagulant Therapy in Sepsis





Take-home Message – 1

- Systemic coagulopathy is intrinsic to systemic inflammation, e.g. sepsis
- Systemic coagulopathy can be attenuated by systemic treatment
- Attenuation of systemic coagulopathy (with APC) benefits patients with severe sepsis

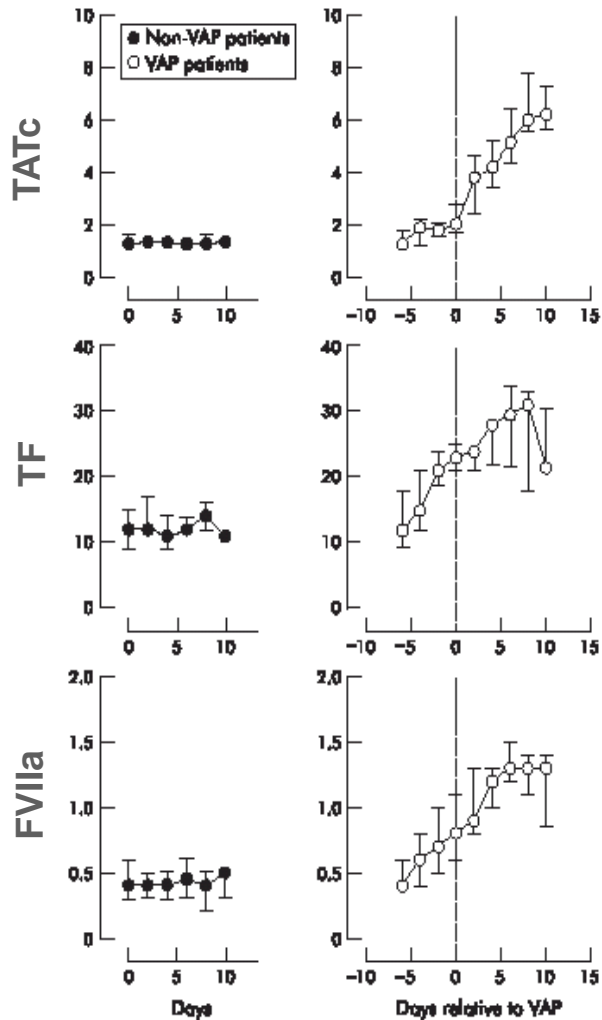


Frame Work of this Presentation

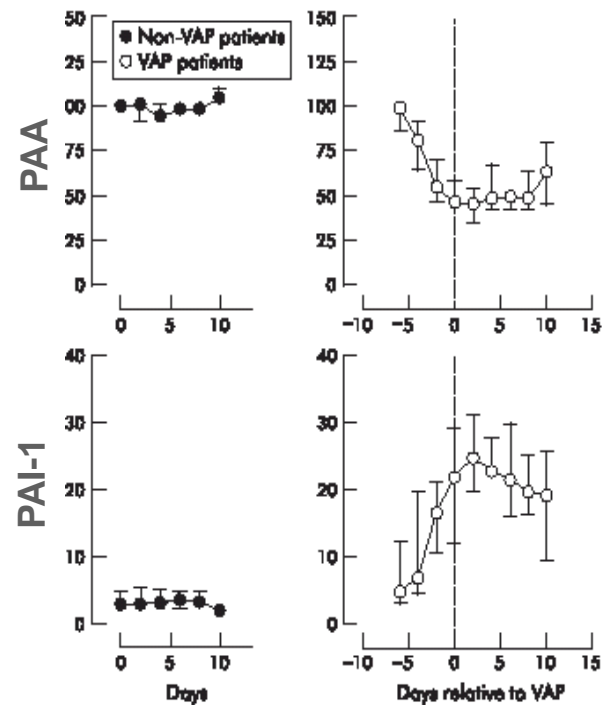
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Coagulopathy with VAP

Coagulation

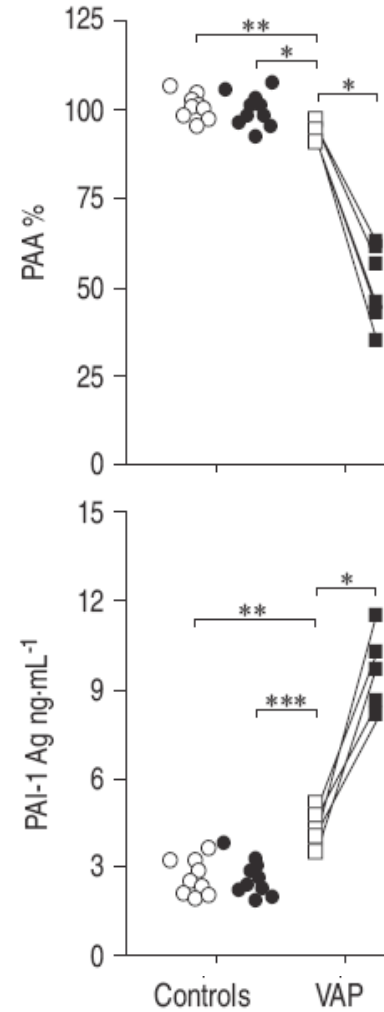
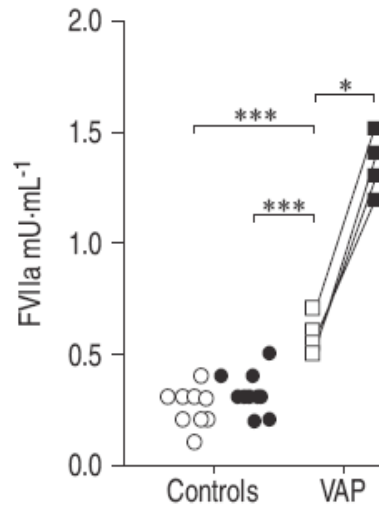
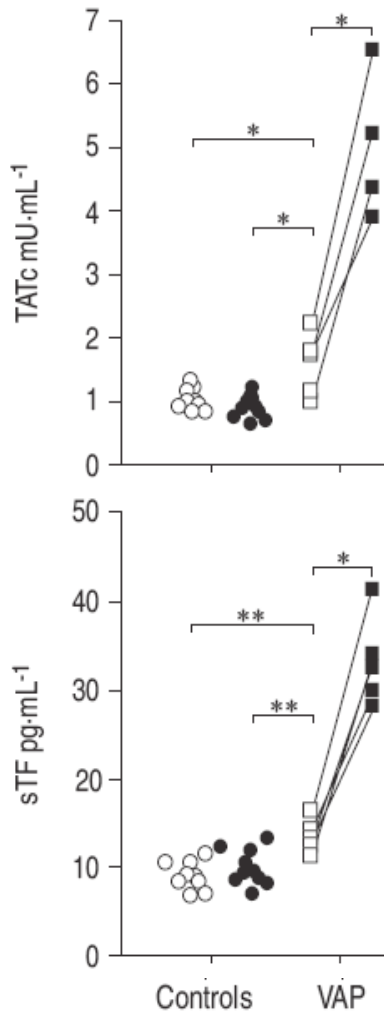


Fibrinolysis



Compartmentalized Coagulopathy

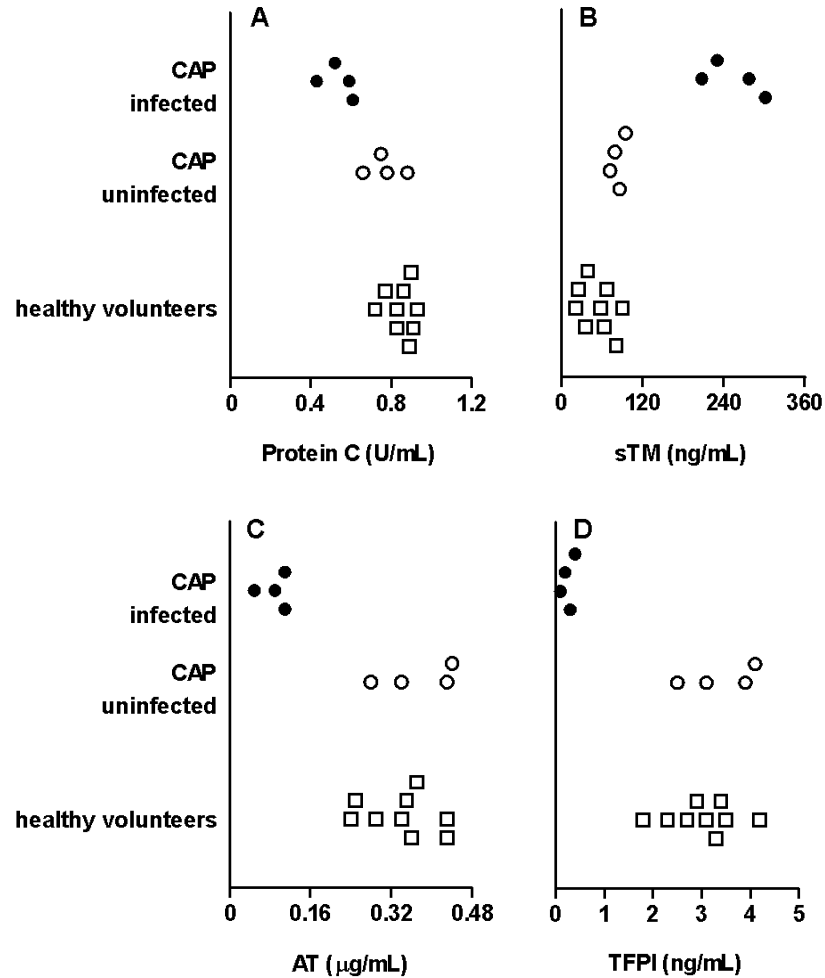
Coagulation



Fibrinolysis

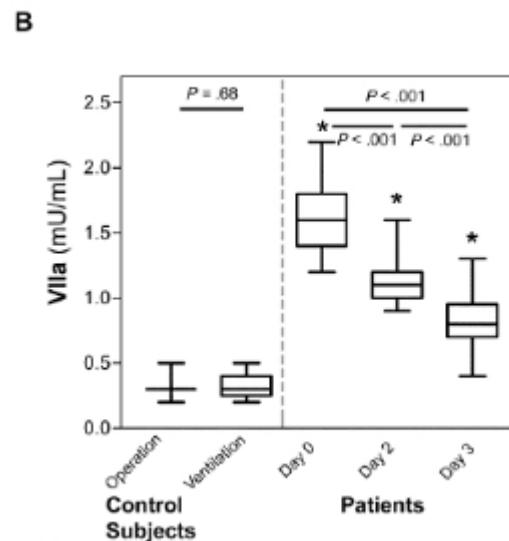
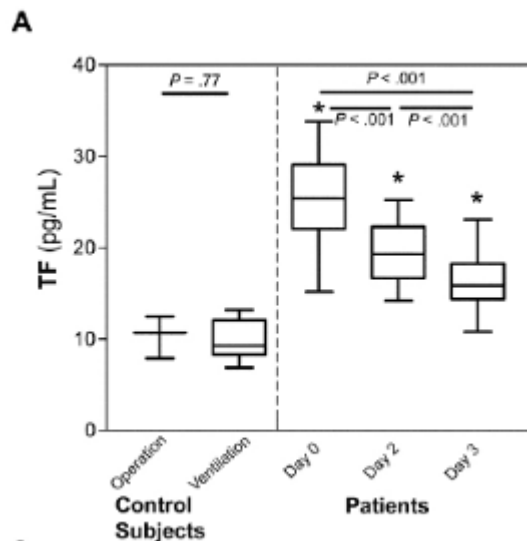
Compartmentalized Coagulopathy

Natural inhibitors

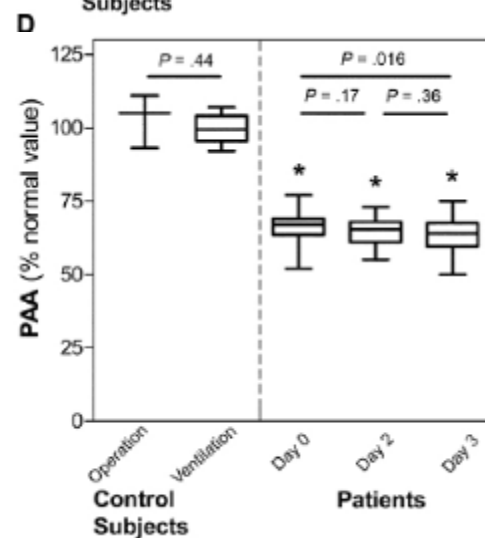
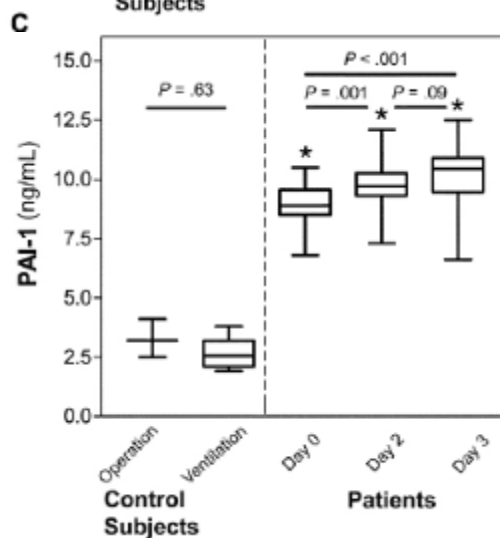


Coagulopathy with SIRS

Coagulation

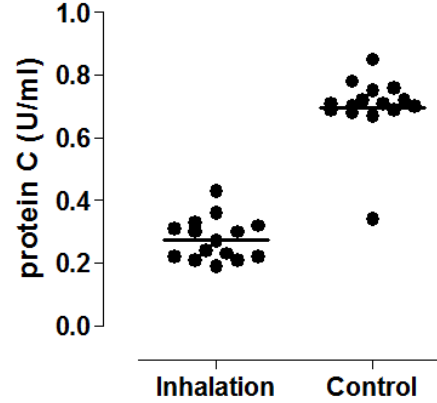
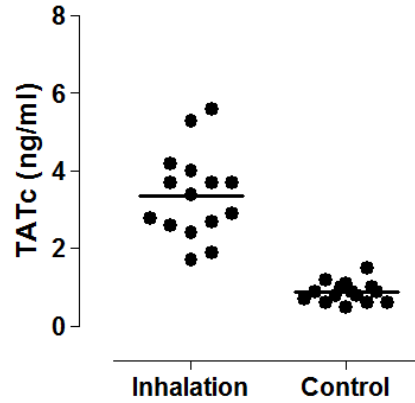


Fibrinolysis



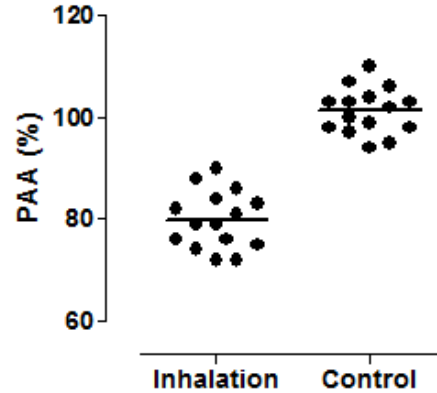
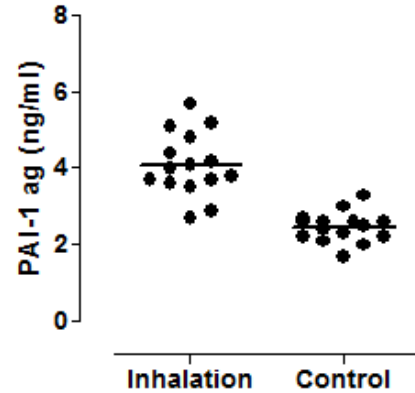
Coagulopathy with Burns

Coagulation



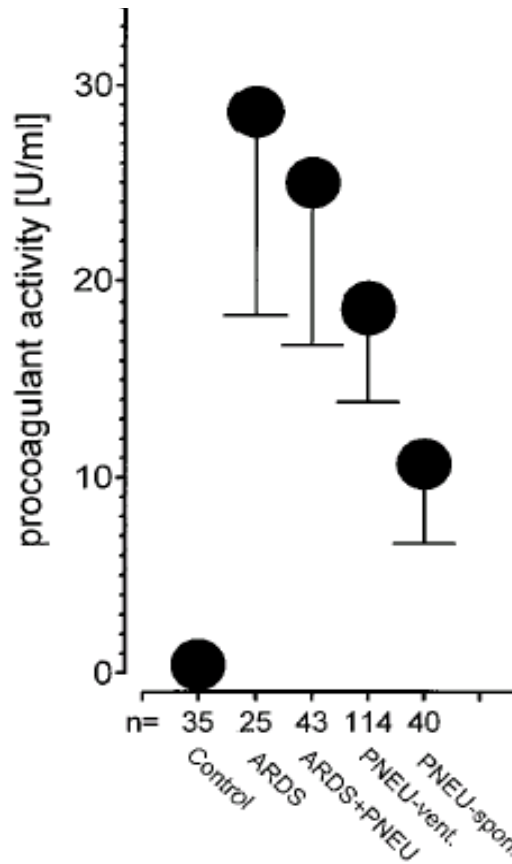
Natural inhibitors

Fibrinolysis

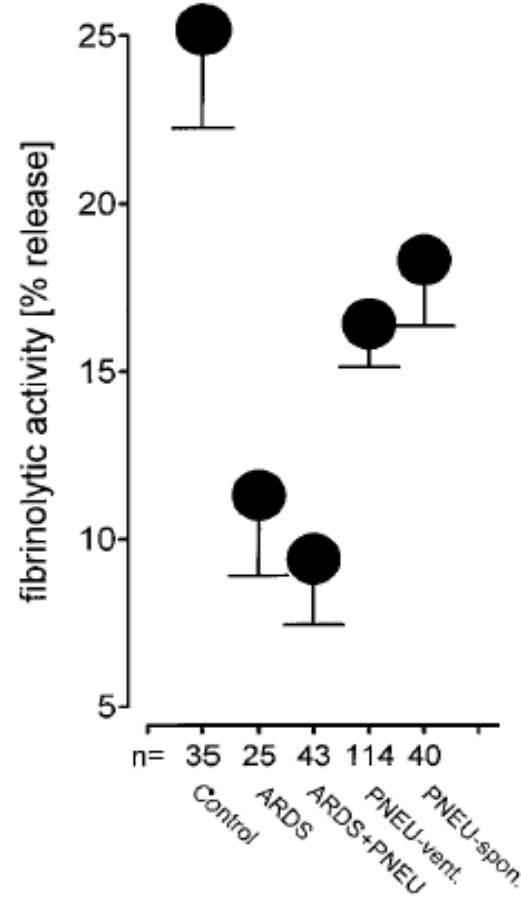


Coagulopathy with ALI/ARDS

Coagulation

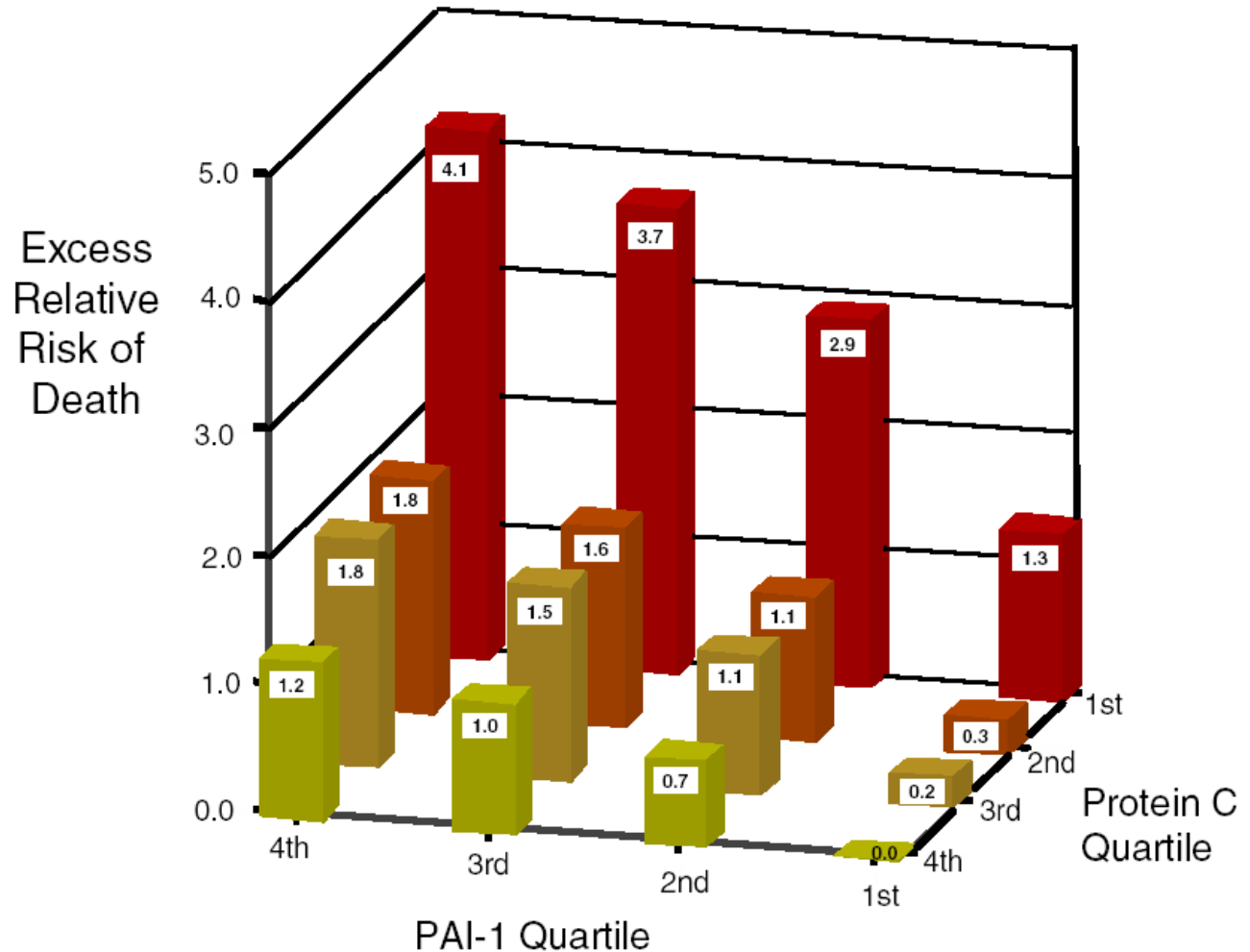


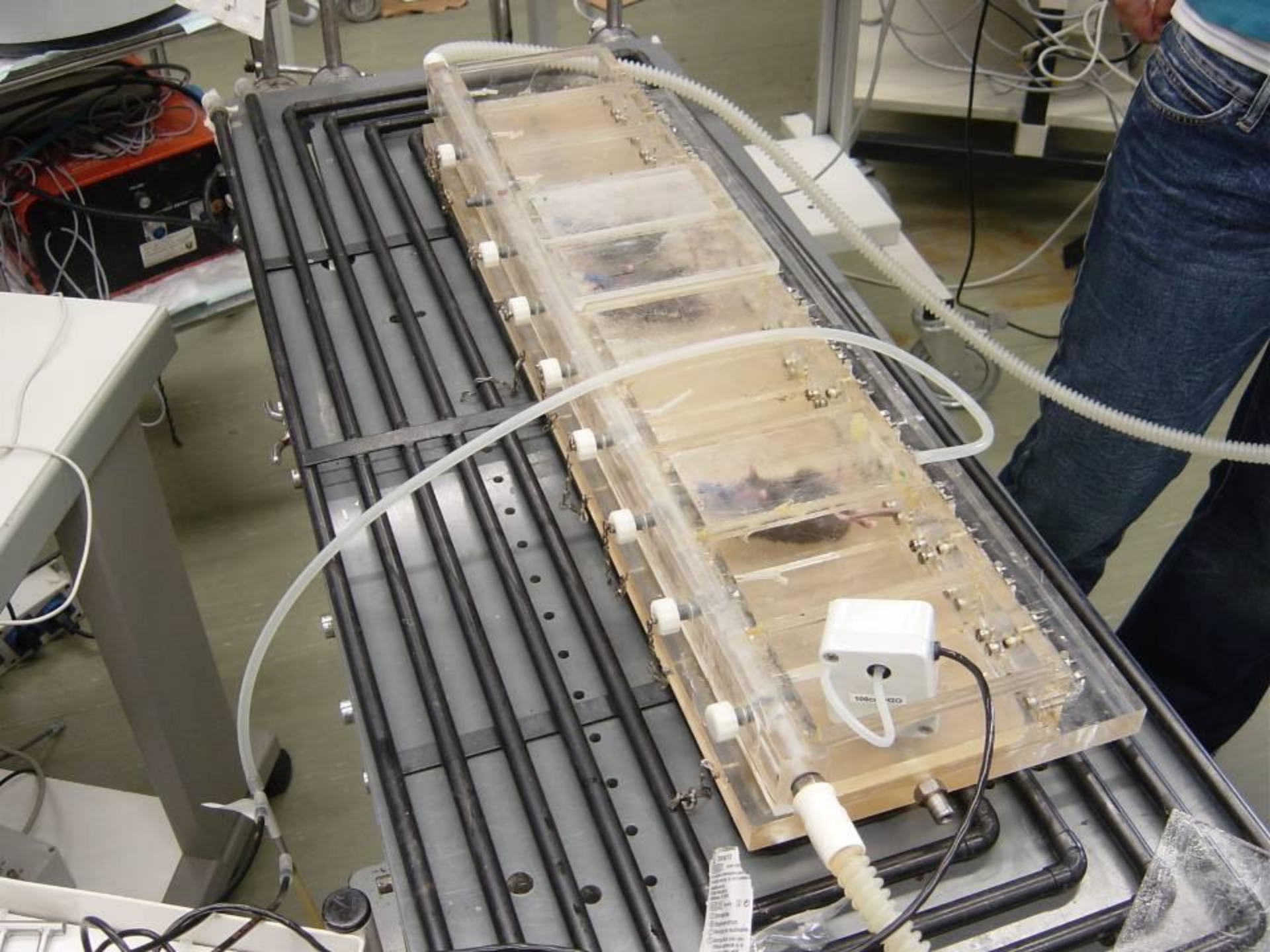
Fibrinolysis





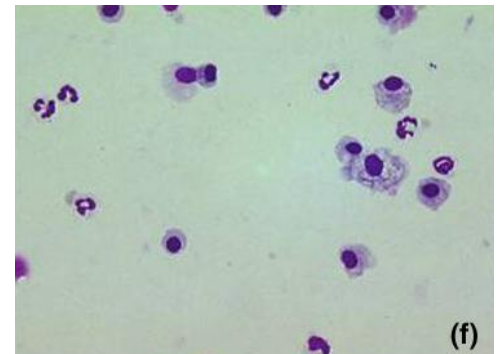
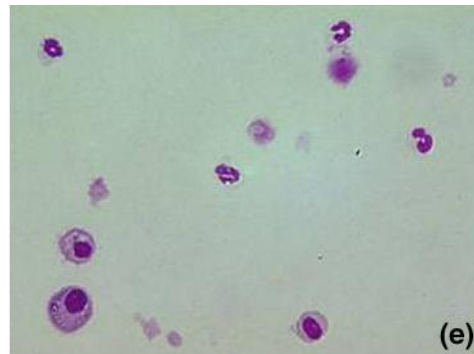
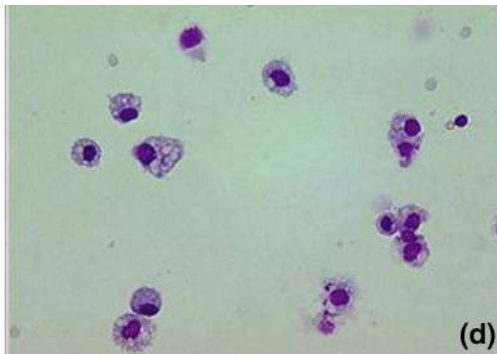
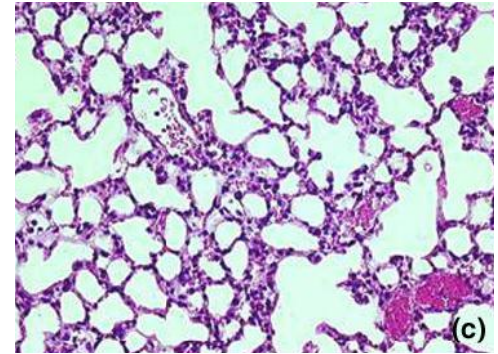
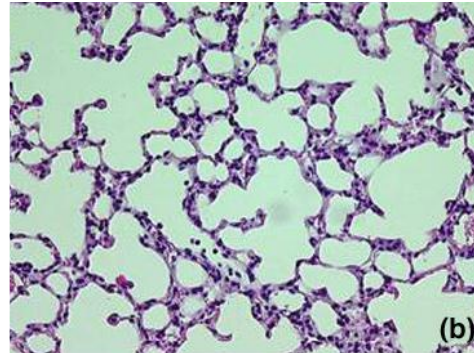
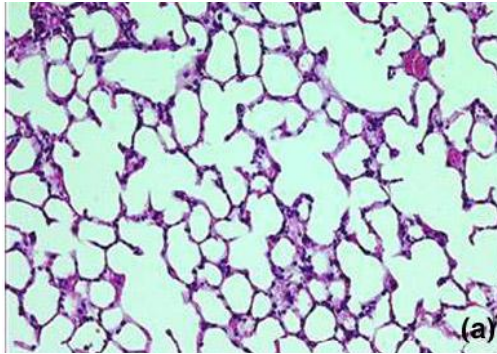
Prognostic Significance of Altered Coagulation in ALI/ARDS







Ventilator-Induced Lung Injury



Control

LVT – lower V_T

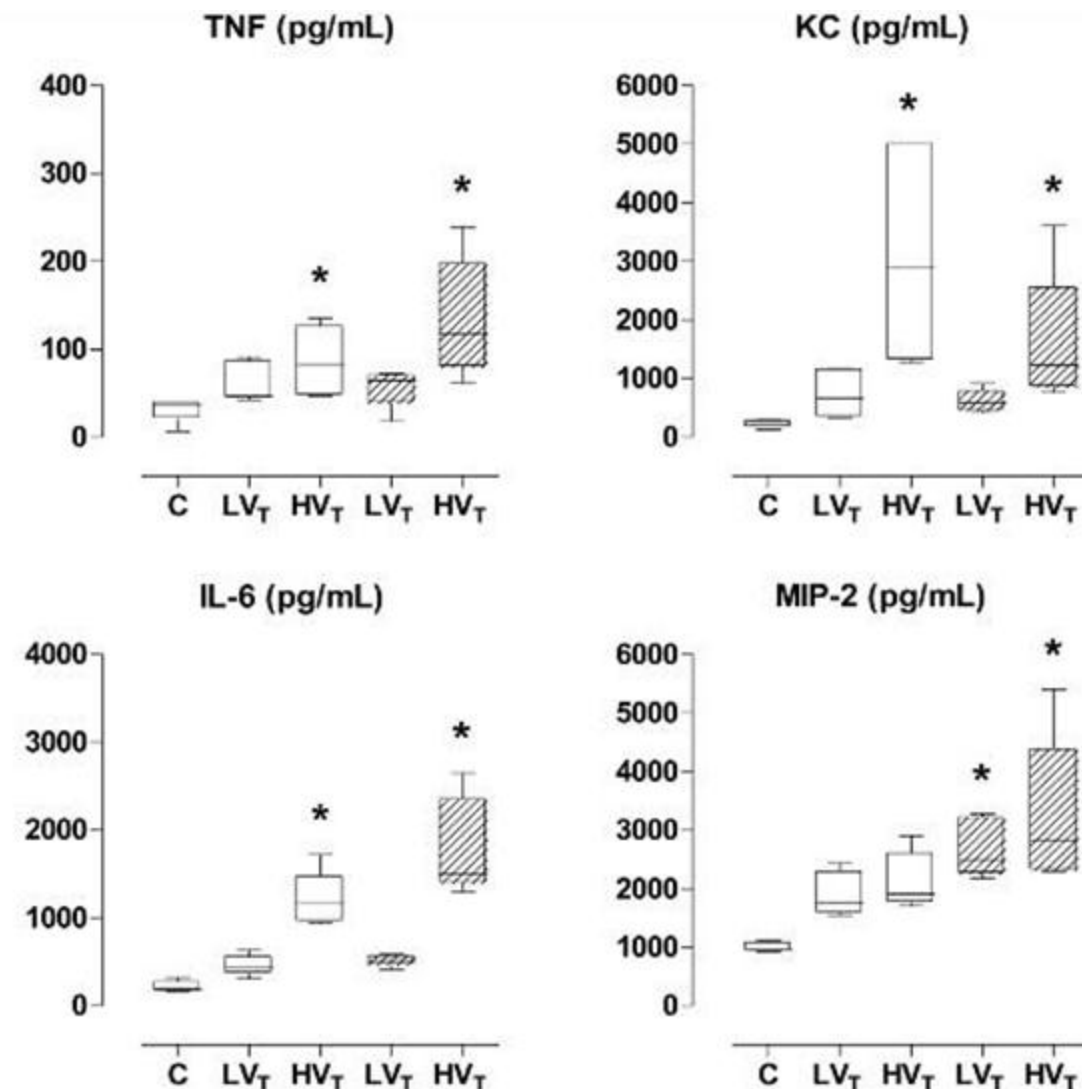
HVT – high V_T



Ventilator-Induced Lung Injury

open boxes – no correction of metabolic acidosis
 ///-hatched boxes – correction of metabolic acidosis

LV_T – lower tidal volumes
 HV_T – high tidal volumes



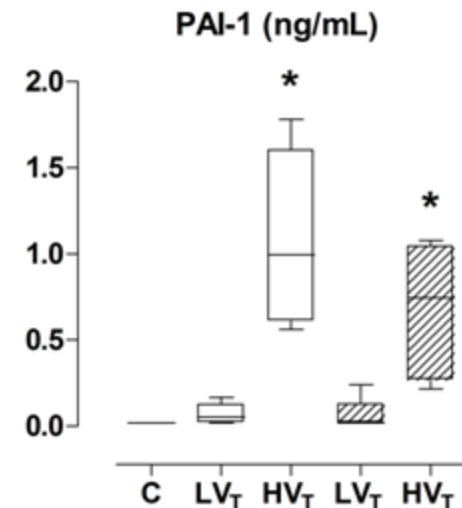
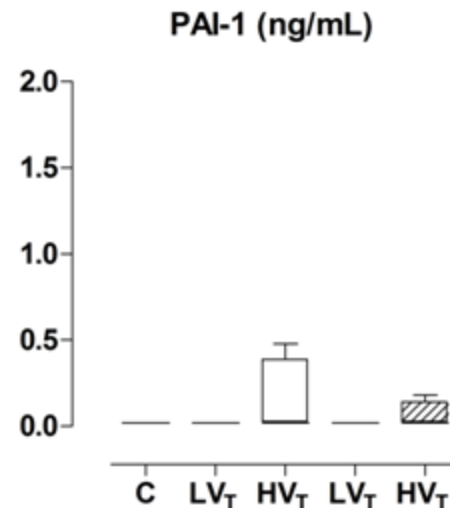
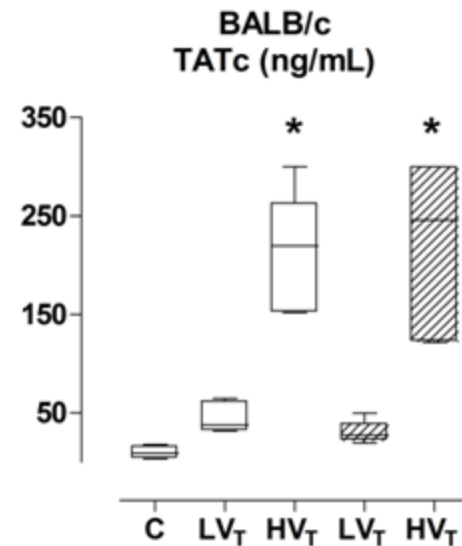
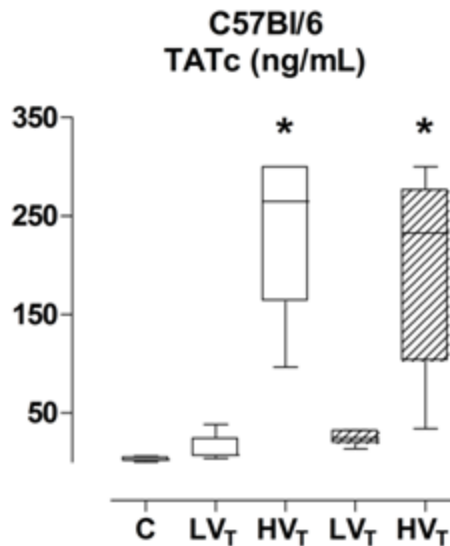
Ventilator-Induced Coagulopathy

Coagulation

open boxes – no correction of metabolic acidosis
 ///-hatched boxes – correction of metabolic acidosis

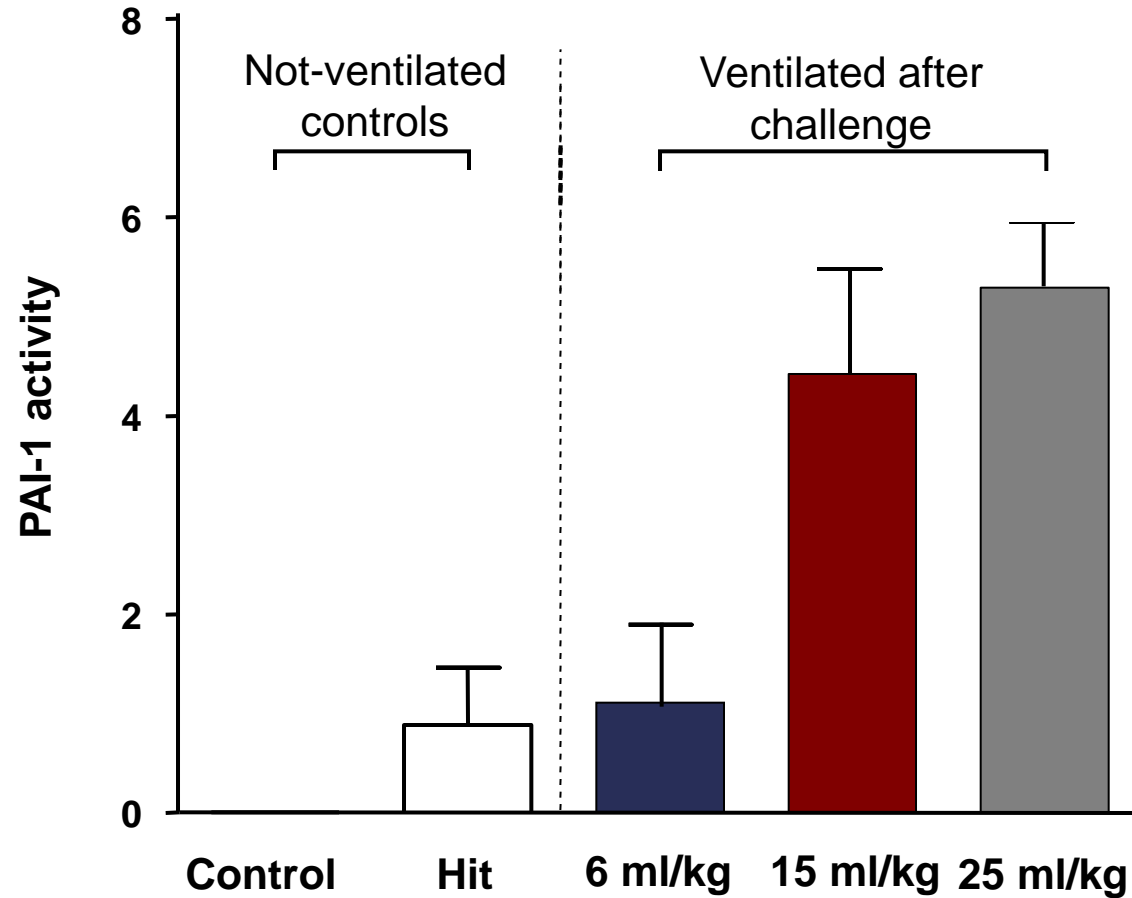
LV_T – lower tidal volumes
 HV_T – high tidal volumes

Fibrinolysis





Ventilator-Induced Coagulopathy



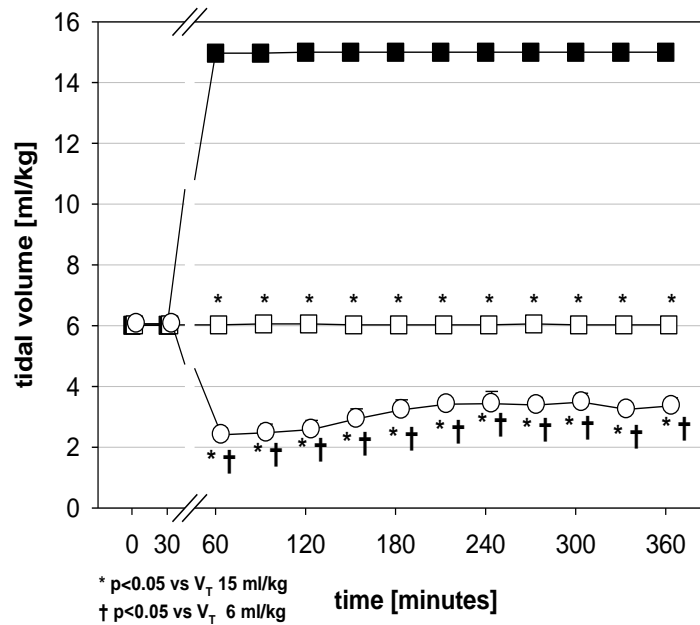




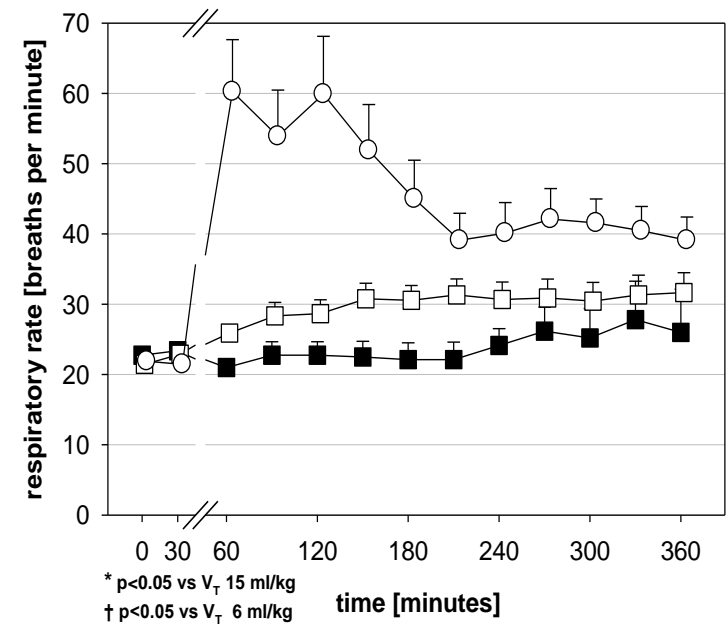
Smaller V_T – Less Coagulopathy?

- V_T 15 ml/kg
- V_T 6 ml/kg
- NAVA

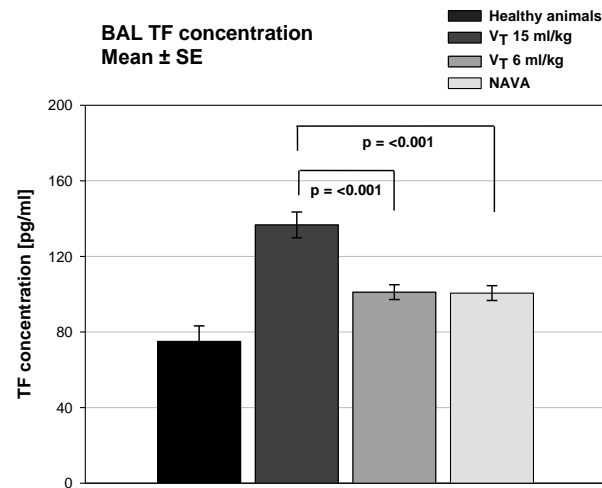
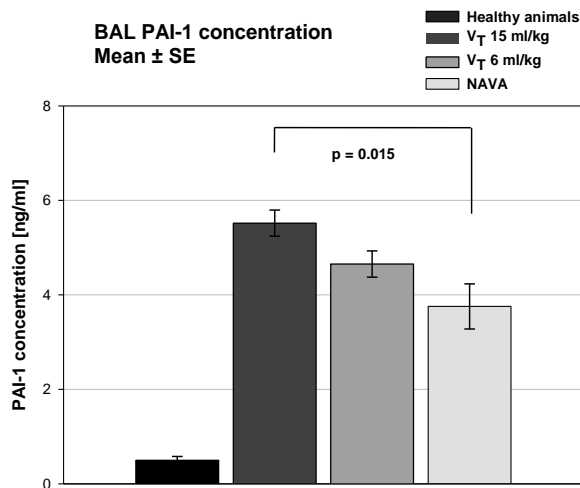
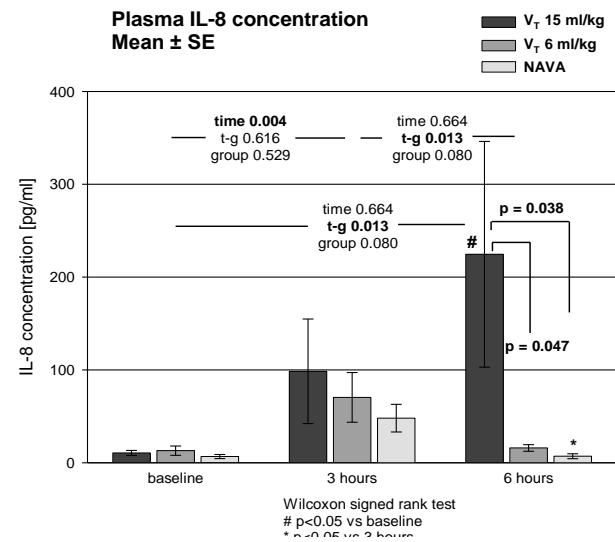
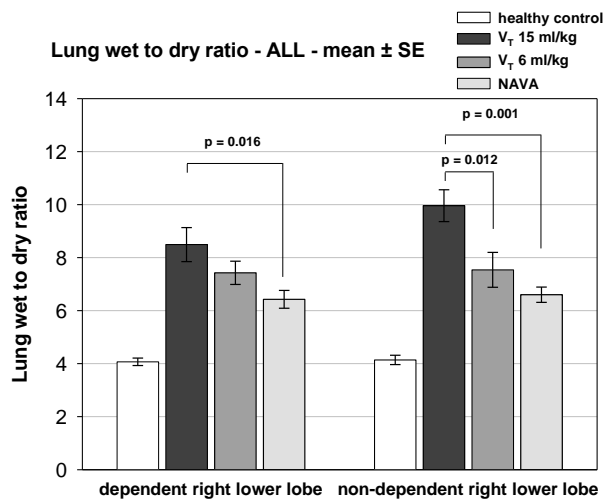
Tidal volume - ALL - mean \pm SEM



Respiratory rate - ALL - mean \pm SEM



NAVA – Coagulopathy



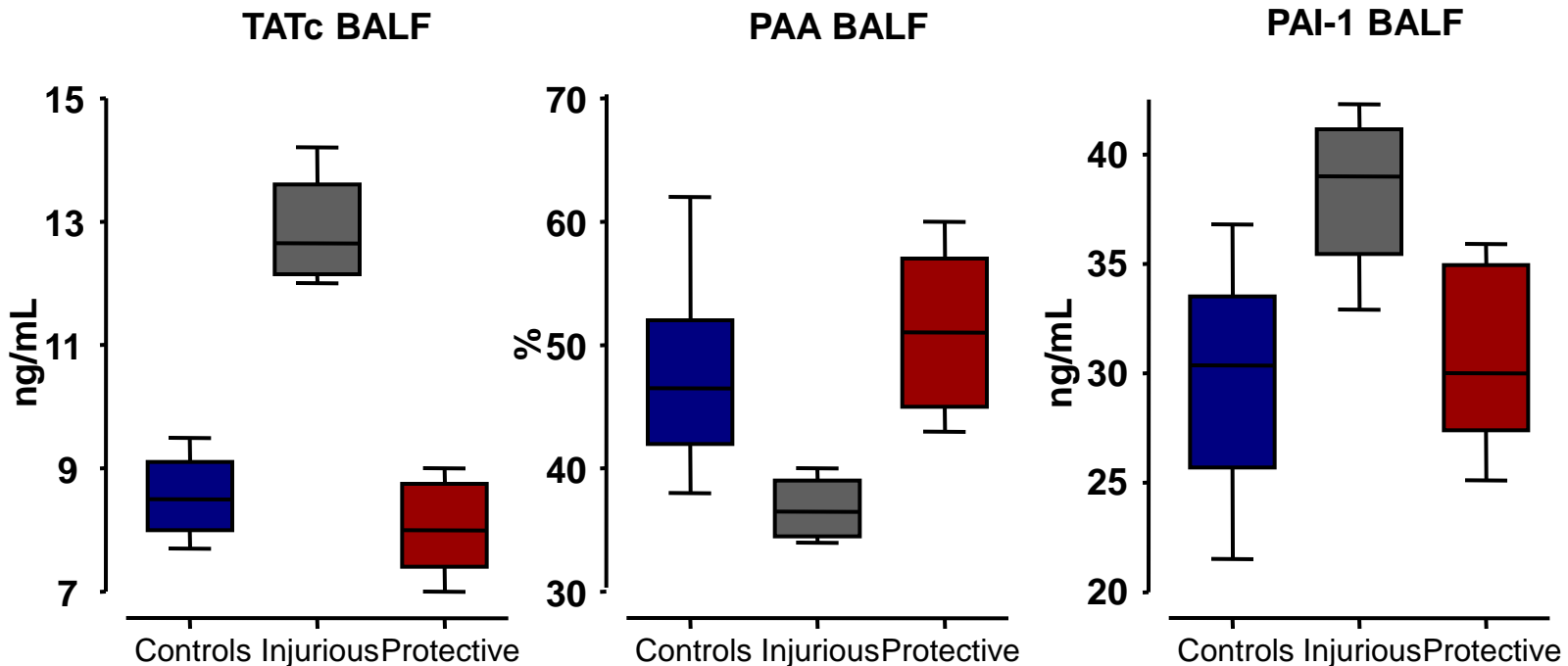
Fibrinolysis

Coagulation

S. pneumoniae Pneumonia

Coagulation

Fibrinolysis



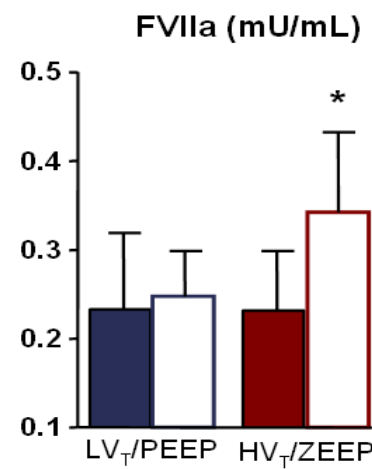
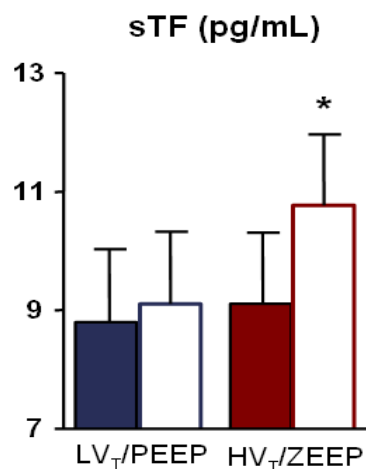
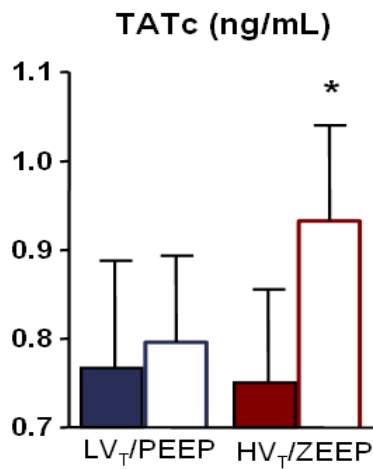
Control: *S. pneumoniae* pneumonia, no MV

Injurious: *S. pneumoniae* pneumonia, HV_T – ZEEP

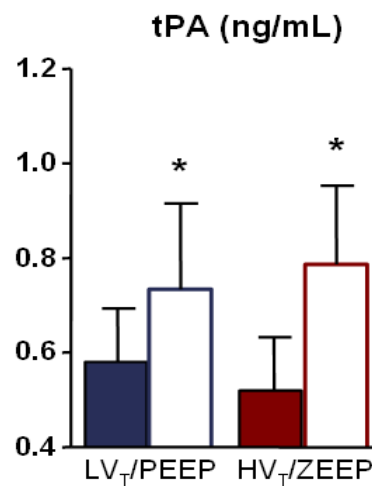
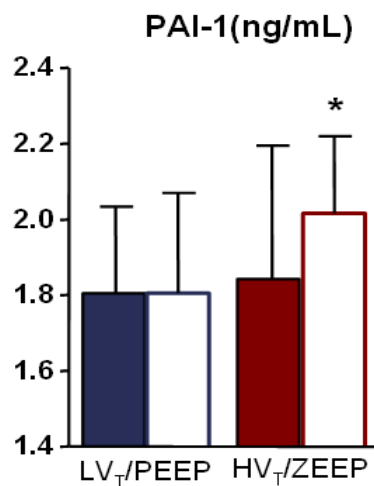
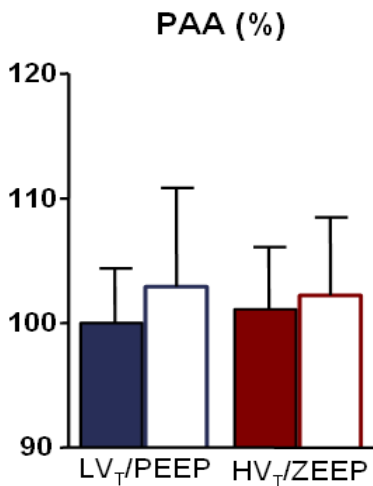
Protective: *S. pneumoniae* pneumonia, LV_T – 5 cm H_2O PEEP

Ventilator-Associated Coagulopathy

Coagulation



Fibrinolysis

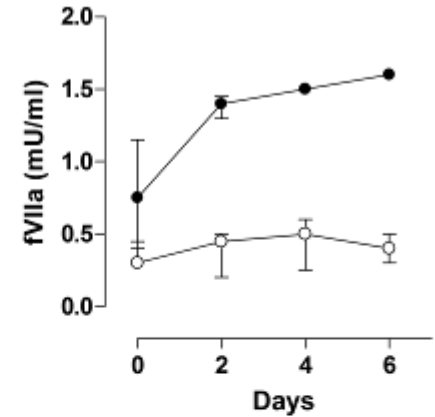
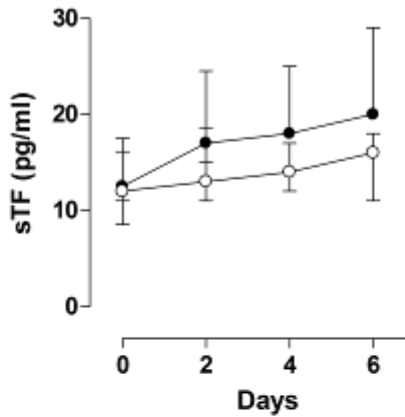
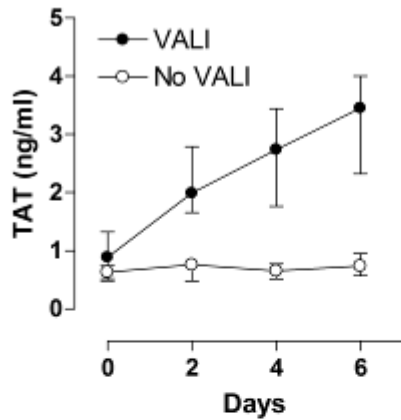


LV_T/PEEP: lung protective
 HV_T/ZEEP: lung injurious

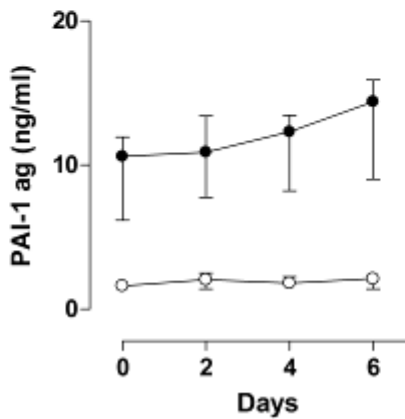
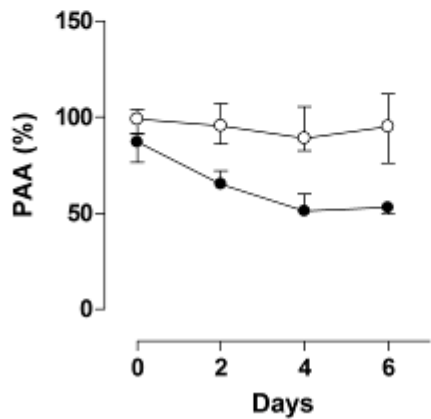
Closed bars: T=0 hours
 Open bars: T=5 hours

Ventilator-Associated Coagulopathy

Coagulation



Fibrinolysis





Take-home Message – 2

- Lung inflammation, whatever its cause (i.e., pneumonia, sepsis, inhalation trauma, mechanical ventilation) is characterized by local coagulopathy
- Local coagulopathy with lung inflammation resembles systemic coagulopathy with sepsis

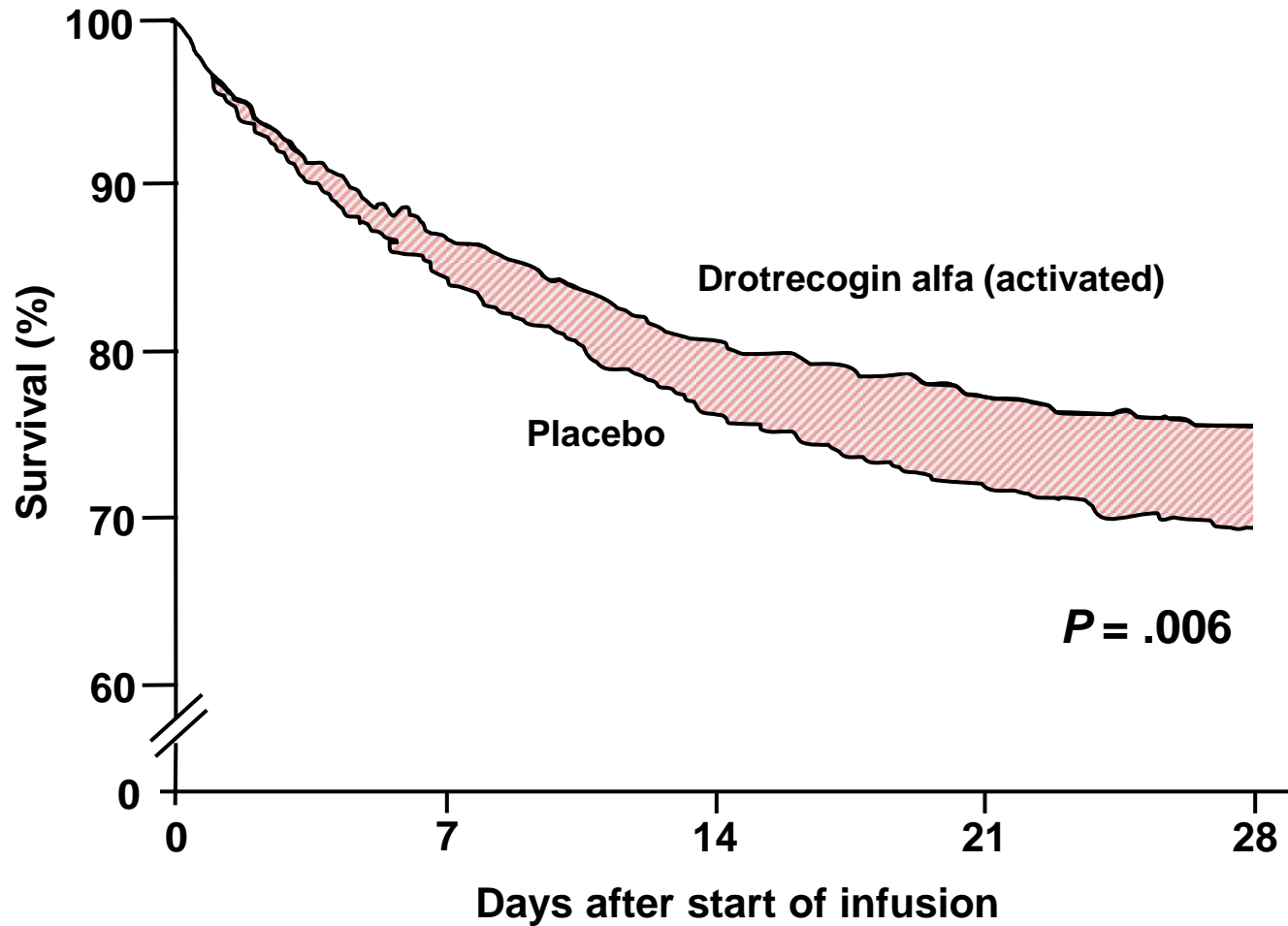


Frame Work of this Presentation

- Systemic coagulation with systemic inflammation
- Local coagulation with pulmonary inflammation
- Rational for anticoagulant strategies for lung injury
- Presently performed *preclinical* studies
- Presently performed *clinical* studies
- Conclusions

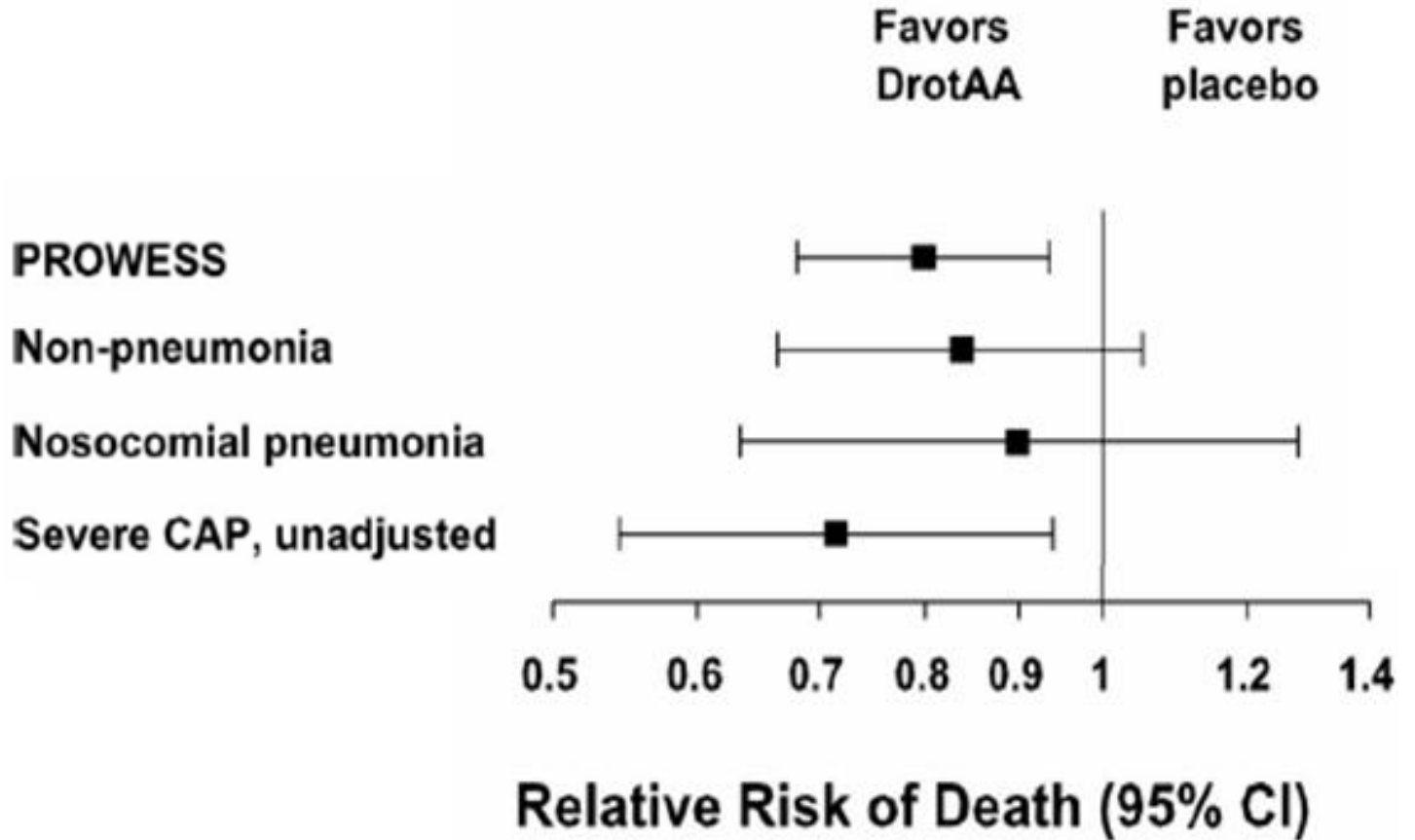


Anticoagulant Therapy in Sepsis





Anticoagulant Therapy in Sepsis



rh-APC and Alveolar Fibrin Turnover after Challenge with LPS

Challenge with:

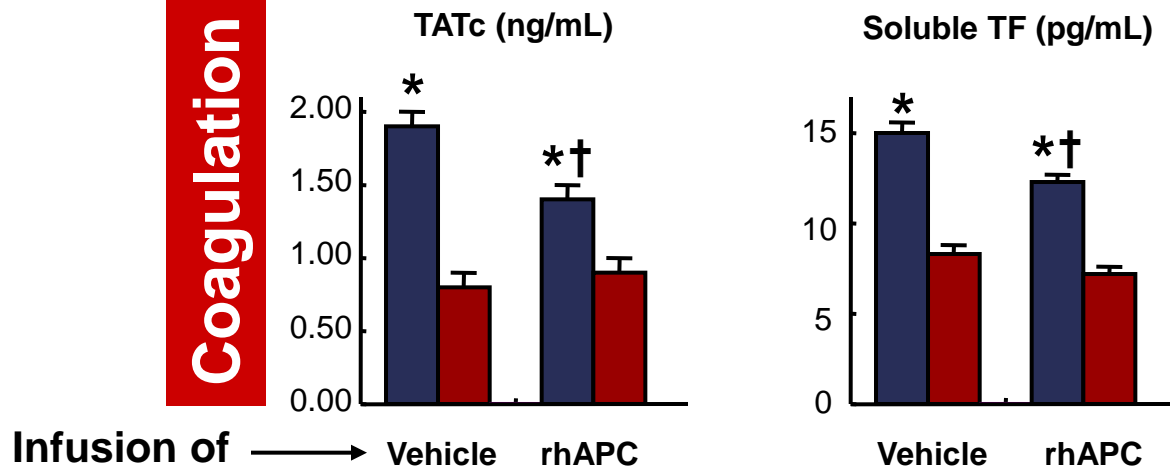
■ Endotoxin

■ Control

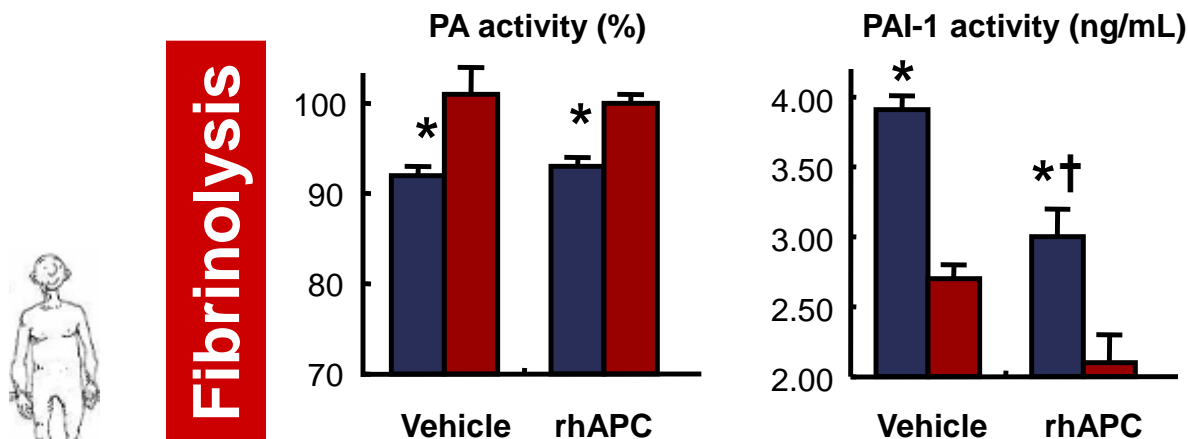
† versus vehicle

* versus control

Coagulation



Fibrinolysis





Take-home Message – 3

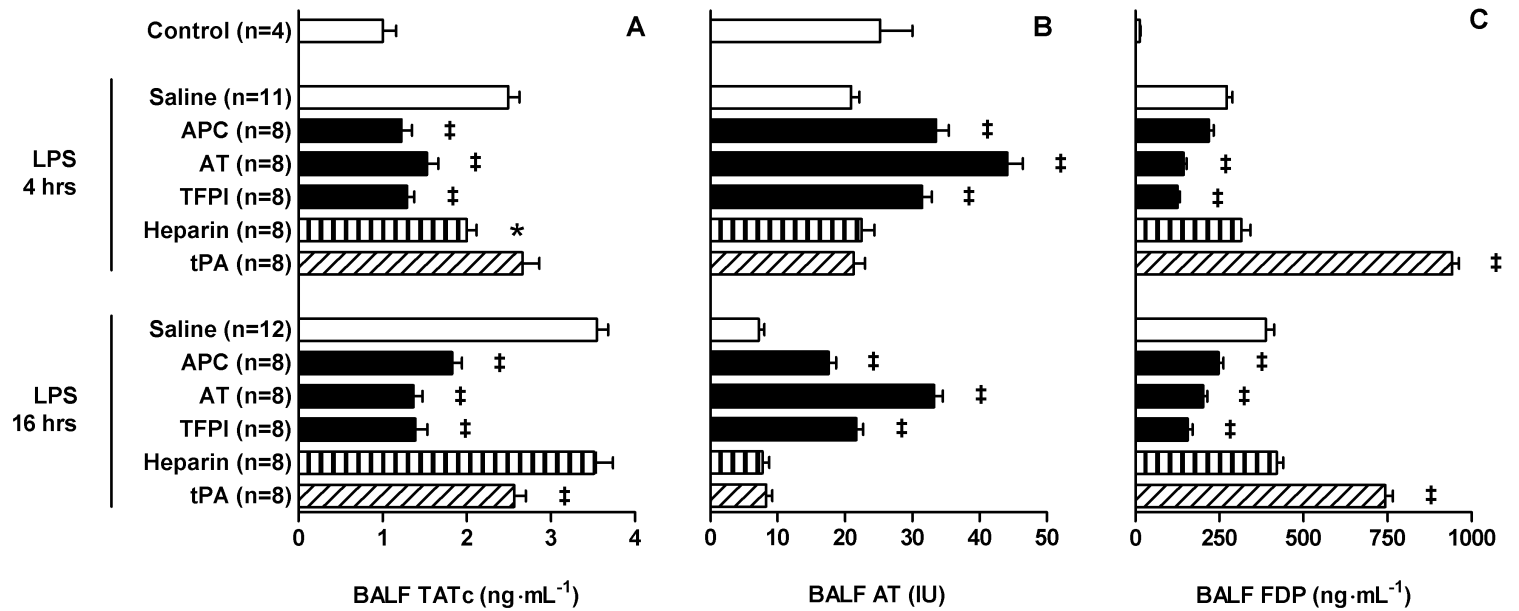
- Local coagulopathy with lung inflammation resembles systemic coagulopathy with sepsis
- Attenuation of local coagulopathy may be beneficial?



Frame Work of this Presentation

- Coagulopathy with systemic inflammation
- Coagulopathy with pulmonary inflammation
- Rational for anticoagulant strategies for lung injury
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- Presently performed *clinical* studies
- Conclusions

Systemic Anticoagulation in ALI Attenuates Pulmonary Coagulopathy

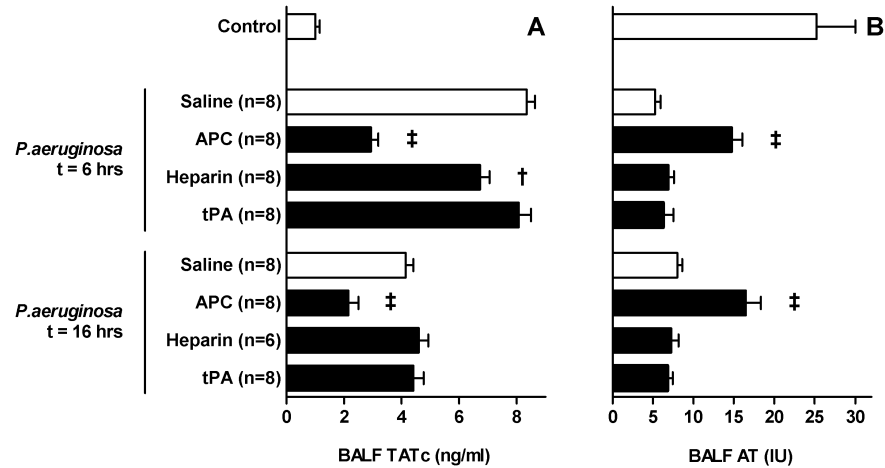


Coagulation

LPS-Induced acute lung injury

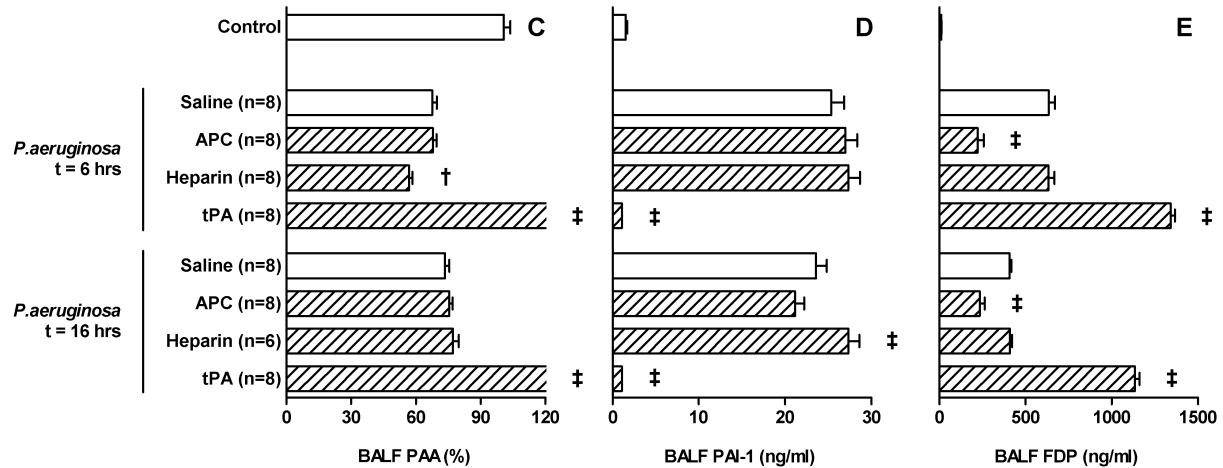
Systemic Anticoagulation in ALI Attenuates Pulmonary Coagulopathy

Coagulation



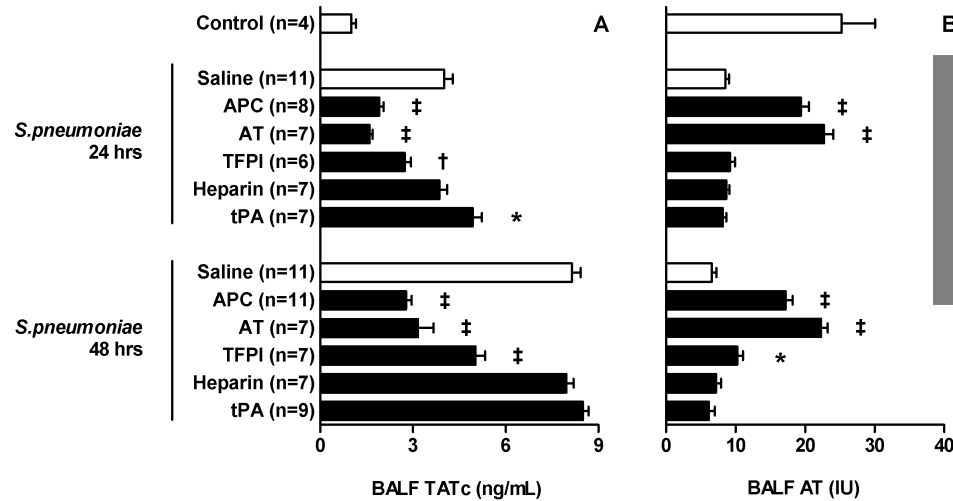
Pseudomonas aeruginosa pneumonia

Fibrinolysis



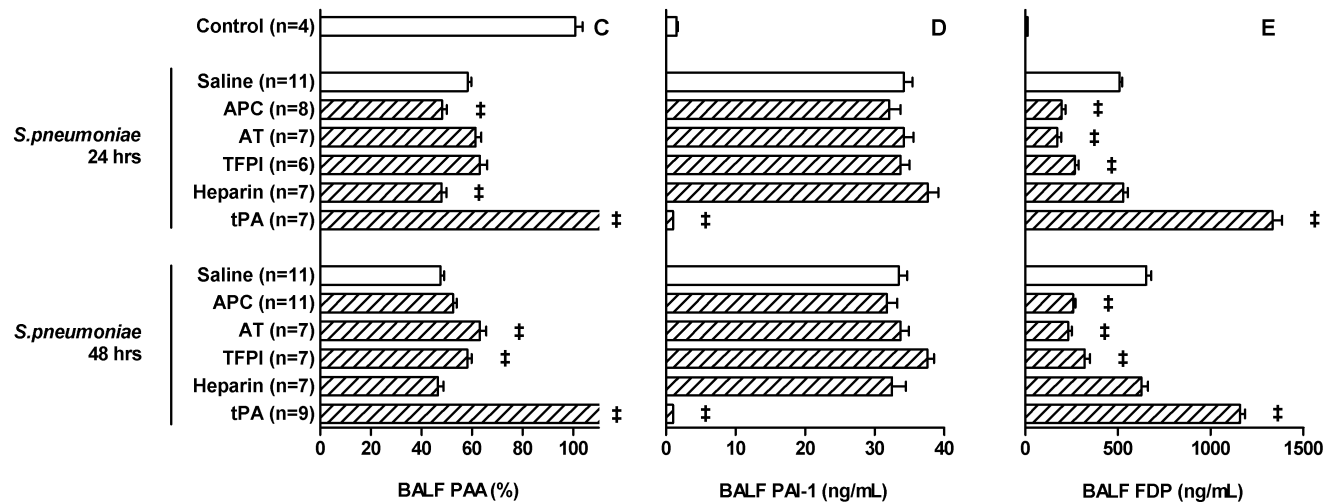
Systemic Anticoagulation in ALI Attenuates Pulmonary Coagulopathy

Coagulation



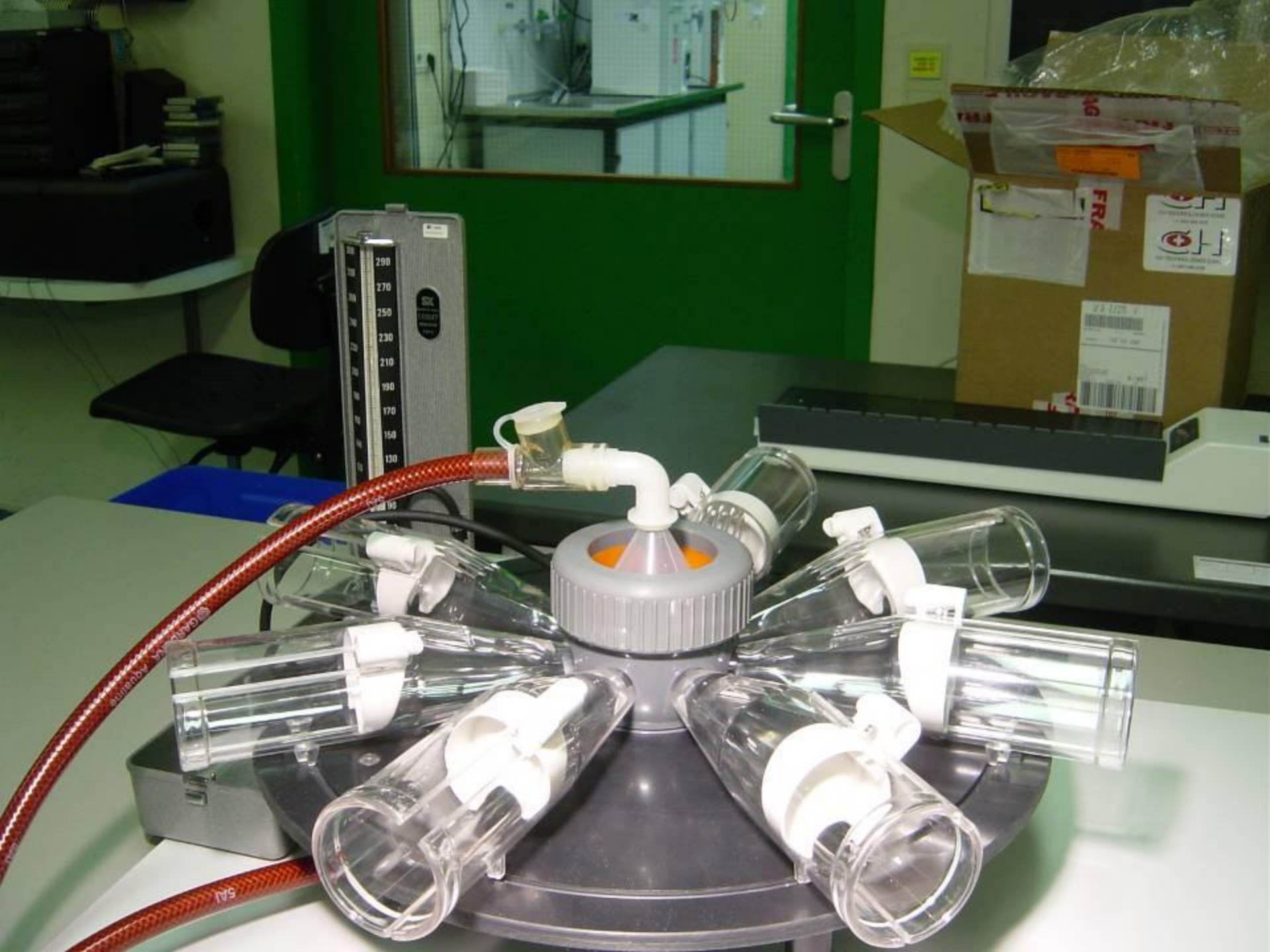
Streptococcus pneumoniae pneumonia

Fibrinolysis



Risk of Anticoagulants Therapy



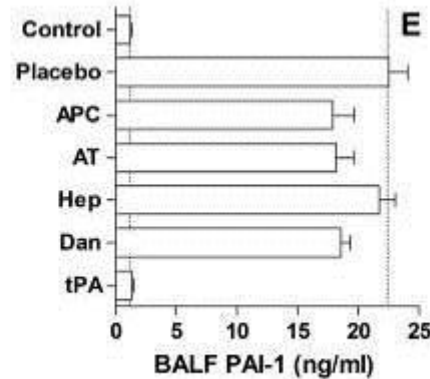
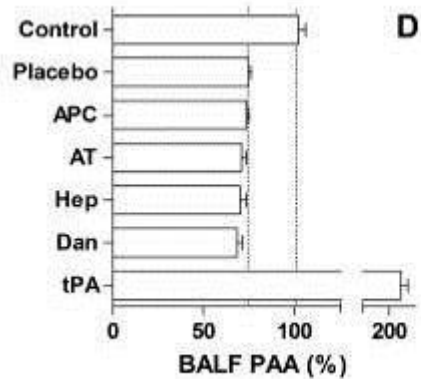
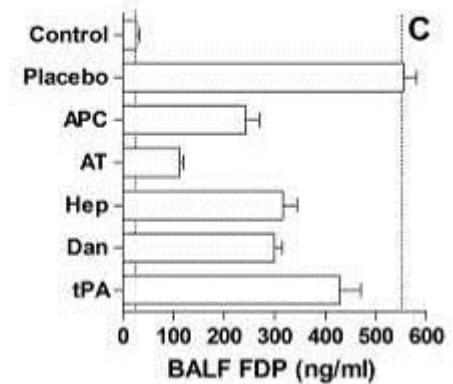
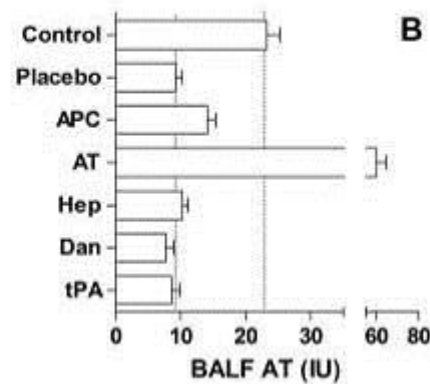
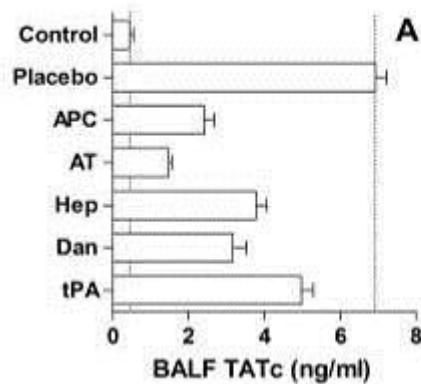






Can *Local* Anticoagulation Therapy Attenuate Pulmonary Coagulopathy?

Coagulation



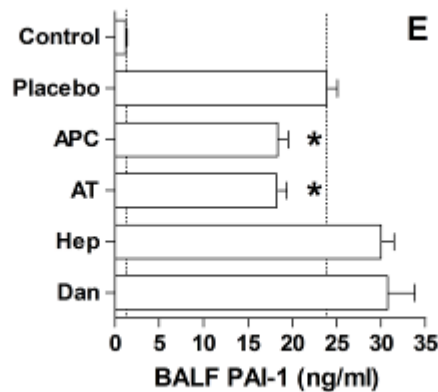
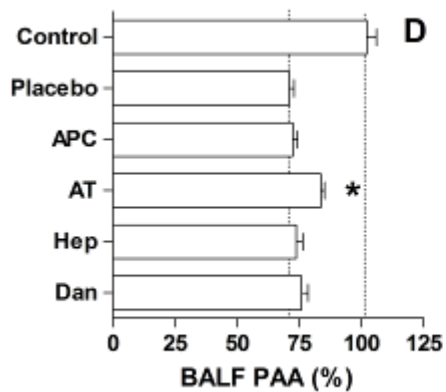
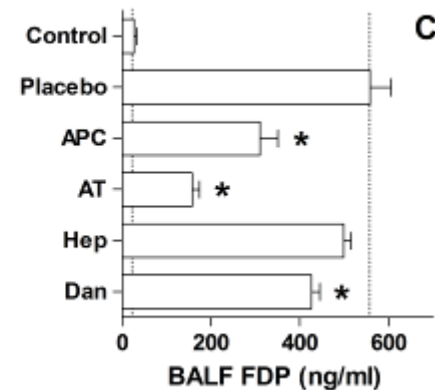
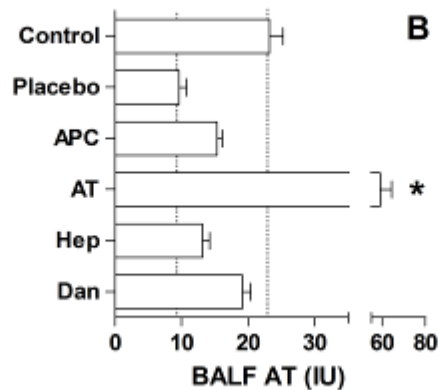
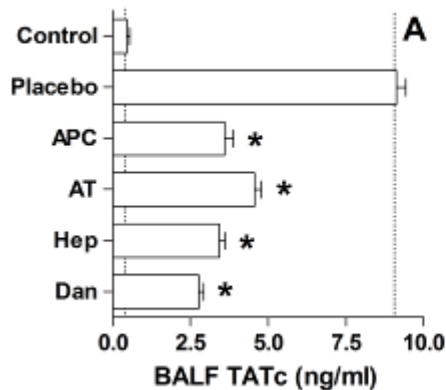
Fibrinolysis

LPS-Induced acute lung injury



Can *Local* Anticoagulation Therapy Attenuate Pulmonary Coagulopathy?

Coagulation



Fibrinolysis

Streptococcus pneumoniae pneumonia



Take-home Message – 4

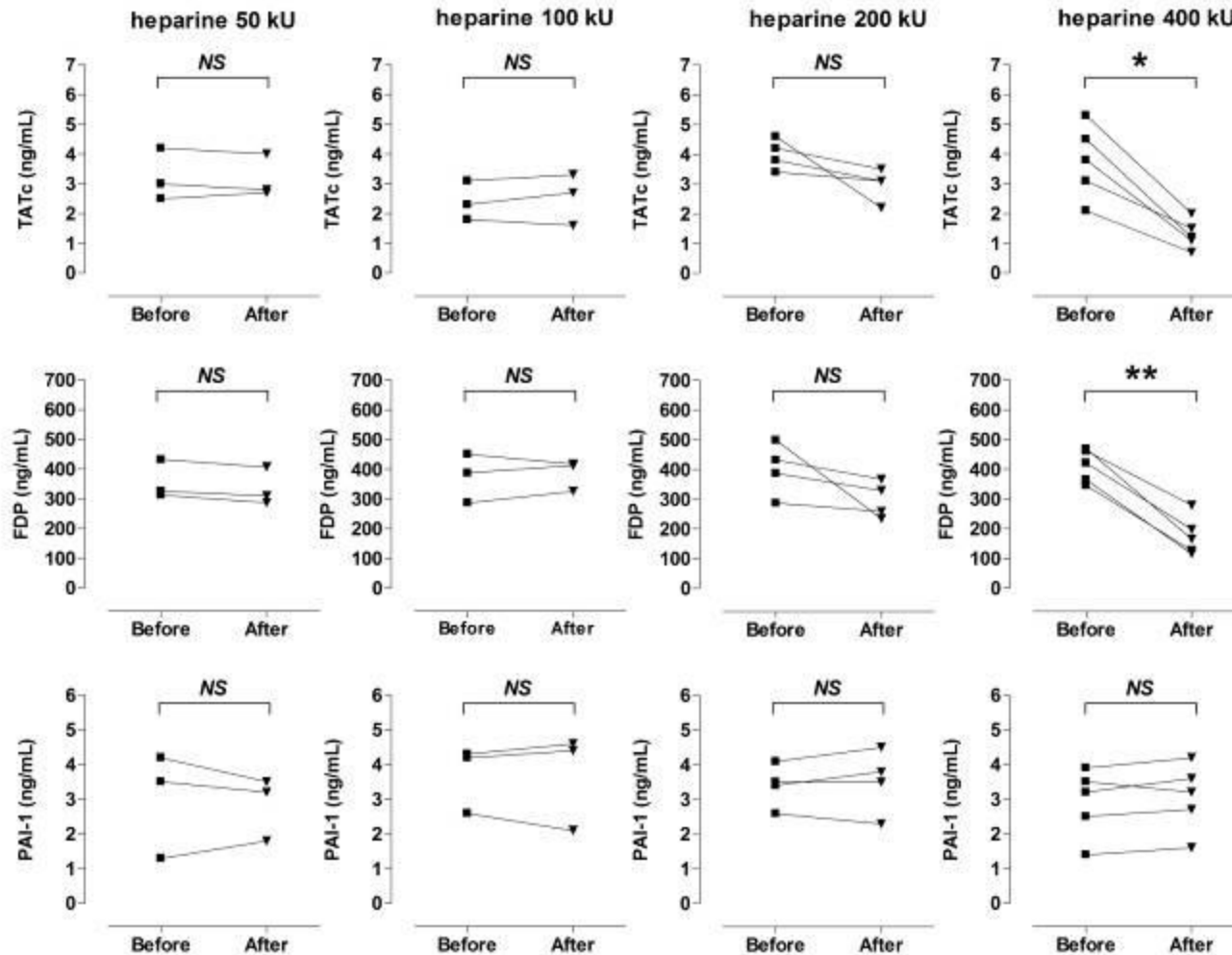
- Local coagulopathy can be attenuated by systemic as well as *local* application of anticoagulants
- Attenuation of pulmonary coagulopathy – attenuation of lung injury in humans?



Frame Work of this Presentation

- Systemic coagulation with systemic inflammation
- Local coagulation with pulmonary inflammation
- Rational for anticoagulant strategies for lung injury
- Presently performed *preclinical* studies
- Presently performed *clinical* studies
- Conclusions

Nebulized heparin in ALI



Heparin cumulative daily dose



Nebulized heparin in acute lung injury

- **Objective:** to determine whether nebulized heparin will result in decrease of inflammation in BAL–fluid (and in reduction of pulmonary vascular permeability)
- **Study population:** 50 intubated and mechanically ventilated patients with ALI/ARDS
- **Intervention** nebulized heparin 100.000 IU every 8 hrs during 24 hrs versus placebo
- **Main study parameters/endpoints:** TATc – and TNF/IL–6 levels in BAL–fluid (and the PLI as a measure of pulmonary vascular permeability)



Frame Work of this Presentation

- Systemic coagulation with systemic inflammation
- Local coagulation with pulmonary inflammation
Rational for anticoagulant strategies for lung injury
- Presently performed *preclinical* studies
- Presently performed *clinical* studies
- Conclusions



Conclusions

- Pulmonary inflammation is characterized by local coagulopathy
- Local coagulopathy resembles systemic coagulopathy with sepsis
- Local coagulopathy can be attenuated by systemic or *local* application of anticoagulants
- Application of *local* anticoagulants may be beneficial