

24. MAJ 2018

DSTH FORÅRSMØDE

AALBORG KONGRES- OG KULTURCENTER | 9000 AALBORG

PATOFYSIOLOGIEN BAG TRAUME-INDUCERET KOAGULOPATI

Jakob Stensballe

Overlæge, Ph.D., Lægefaglig ansvarlig for Reg H's Blødningsvagt
Anæstesi og operationsklinikken & TraumeCenter, HOC

&

Transfusionsmedicinsk Enhed, Blodbanken i Region Hovedstaden
Rigshospitalet

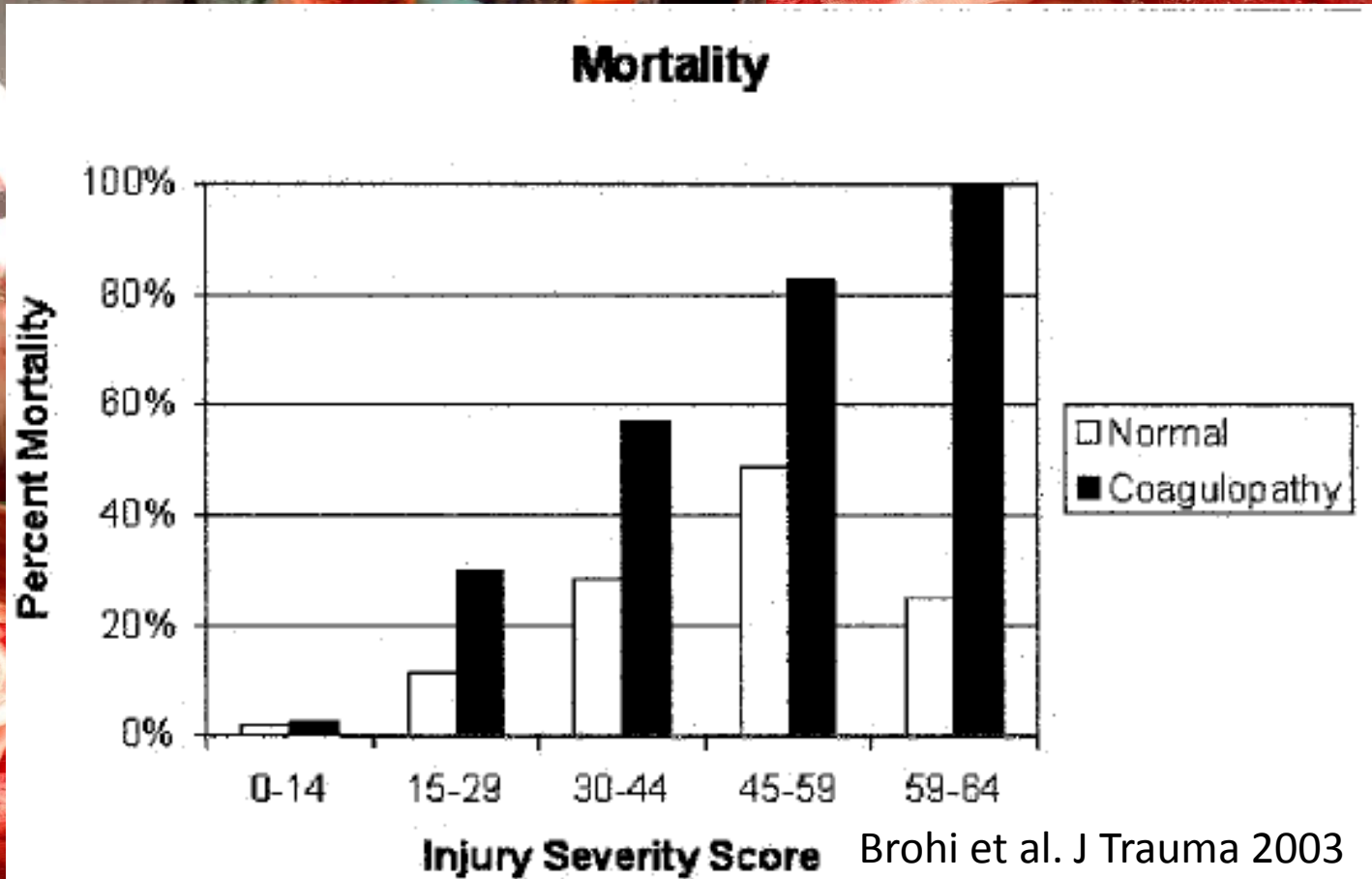
stensballe@rh.dk

COI: None

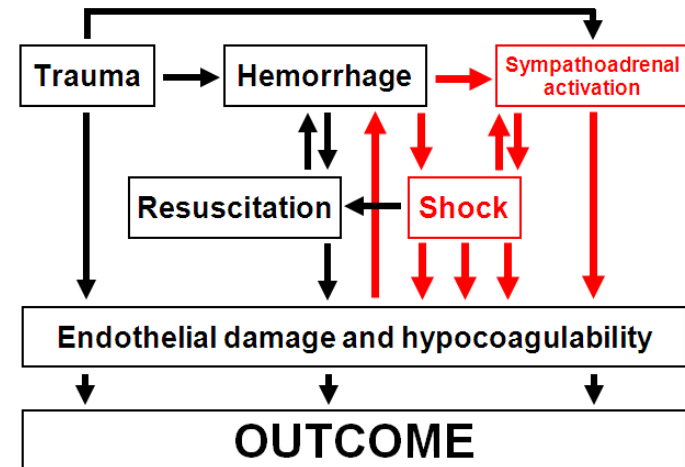
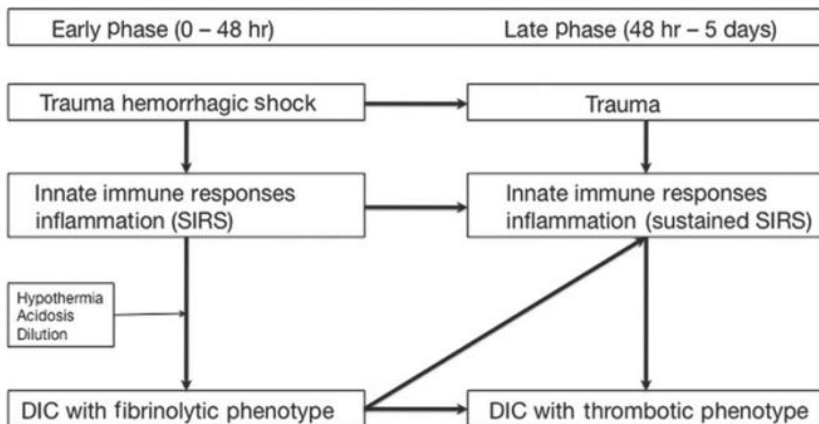
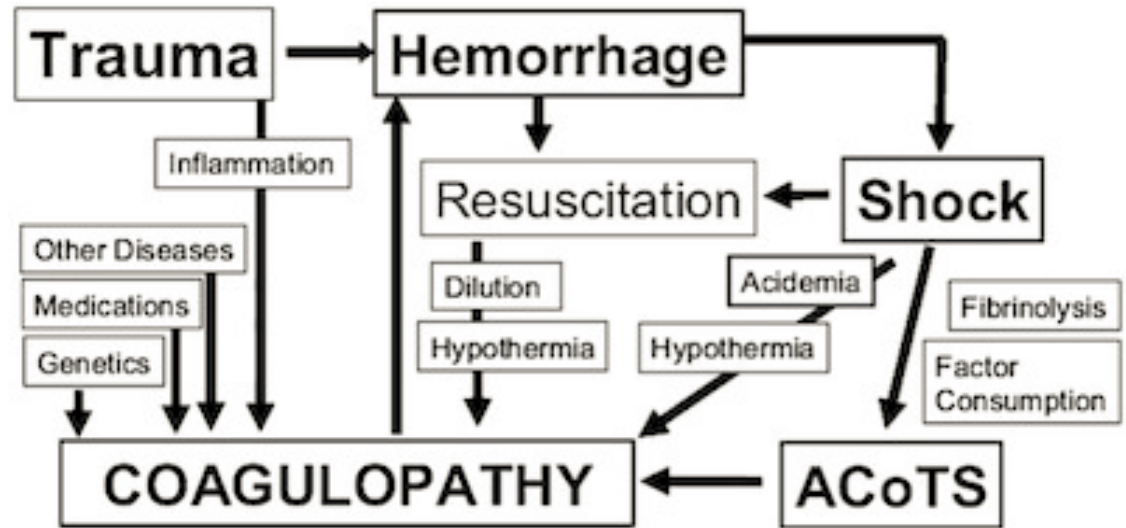
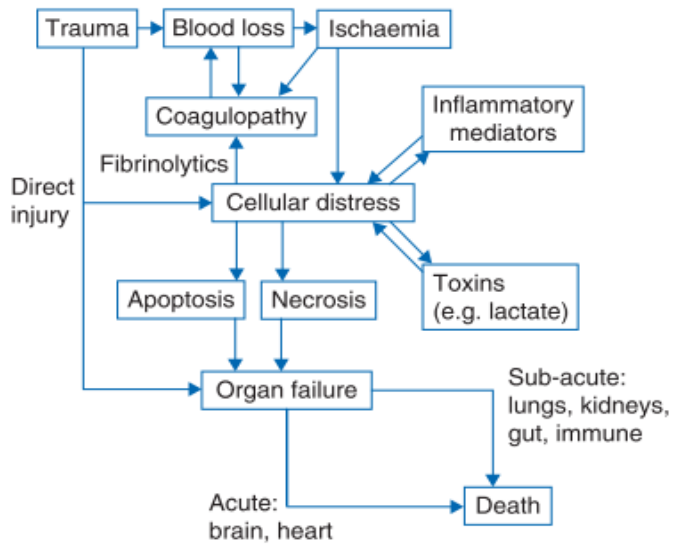




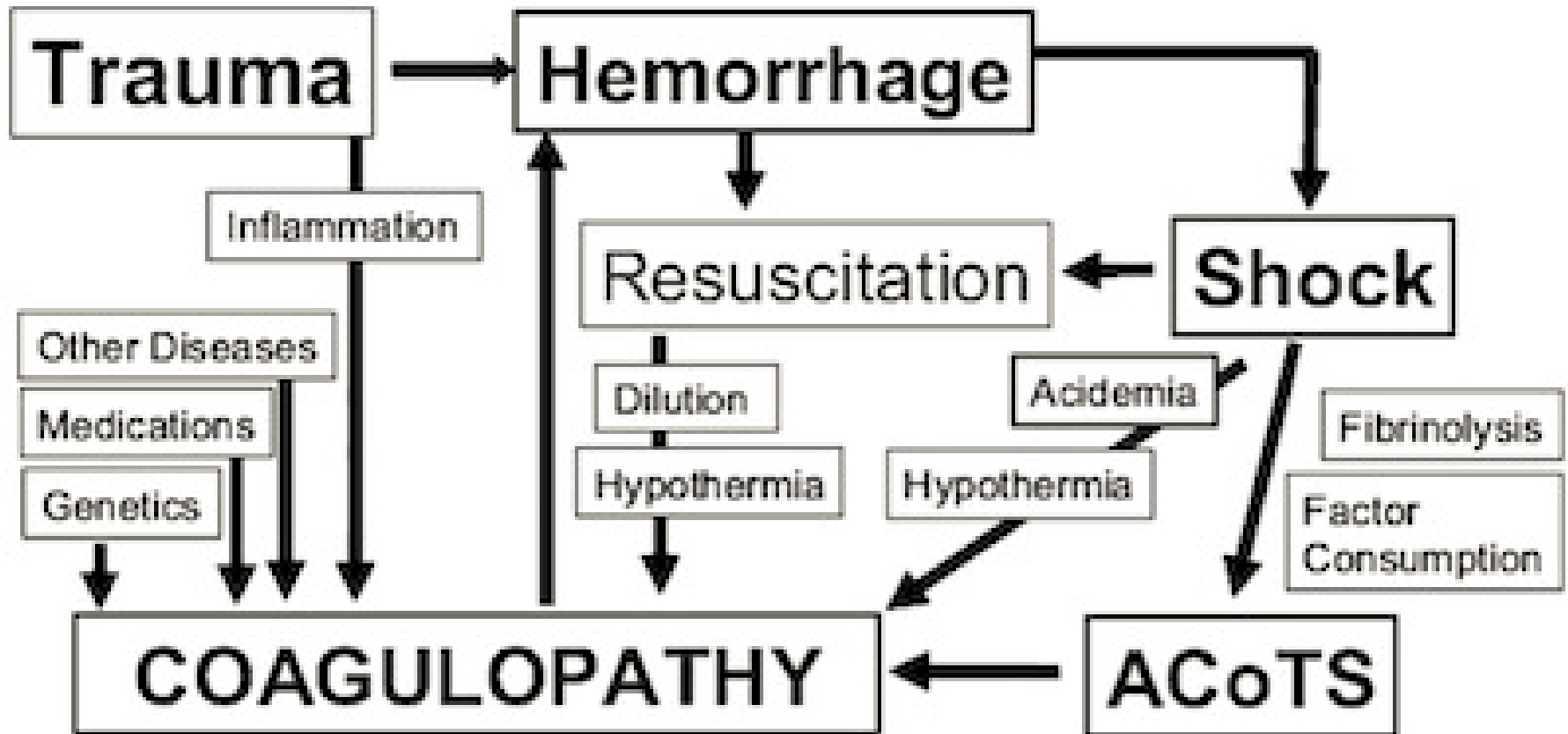
TRAUME-INDUCERET KOAGULOPATI



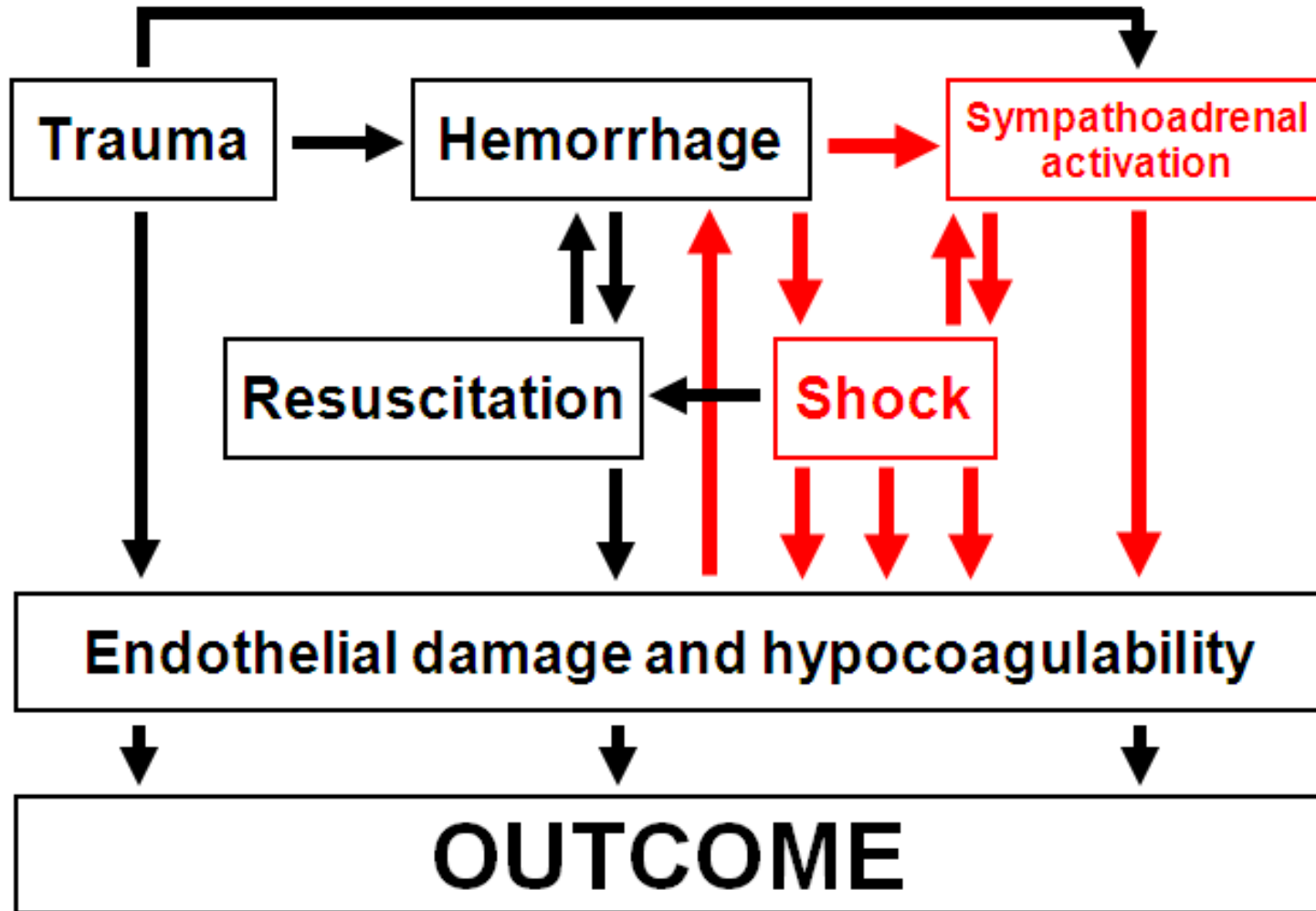
TRAUME-INDUCERET KOAGULOPATI

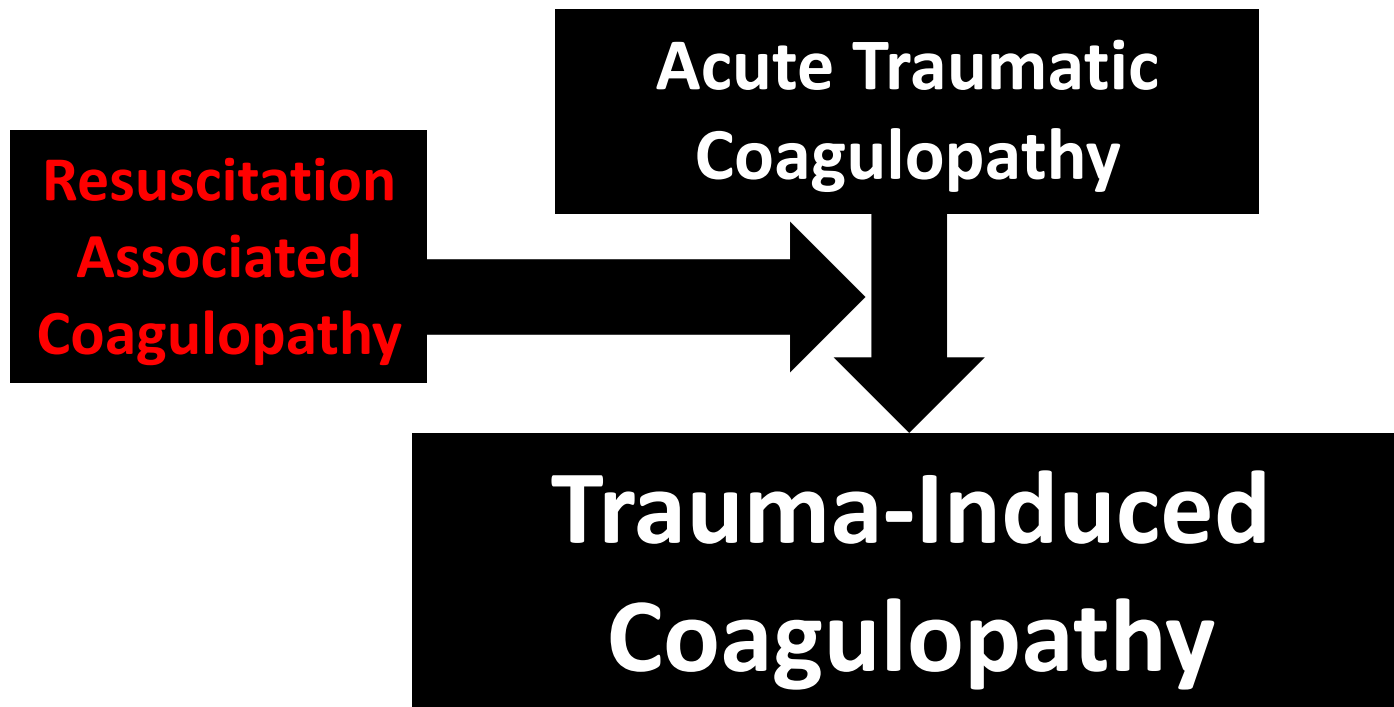


TRAUME-INDUCERET KOAGULOPATI



TRAUME-INDUCERET KOAGULOPATI







Trauma

Shock

Hemorrhage

Systemic Endotheliopathy

Endogenous
Heparinization

Activated
Protein C

Hyper-
fibrinolysis

Platelet
Dysfunction

**Acute Traumatic
Coagulopathy**

**Resuscitation
Associated
Coagulopathy**

**Trauma-Induced
Coagulopathy**

Stensballe et al.
Curr Opin of Crit
Care. 2017.

TRAUME-INDUCERET KOAGULOPATI

Minor trauma
ISS 0-10



Normal TEG

Moderate trauma
ISS 10-20



Hypercoagulability

Severe trauma
ISS 20-35



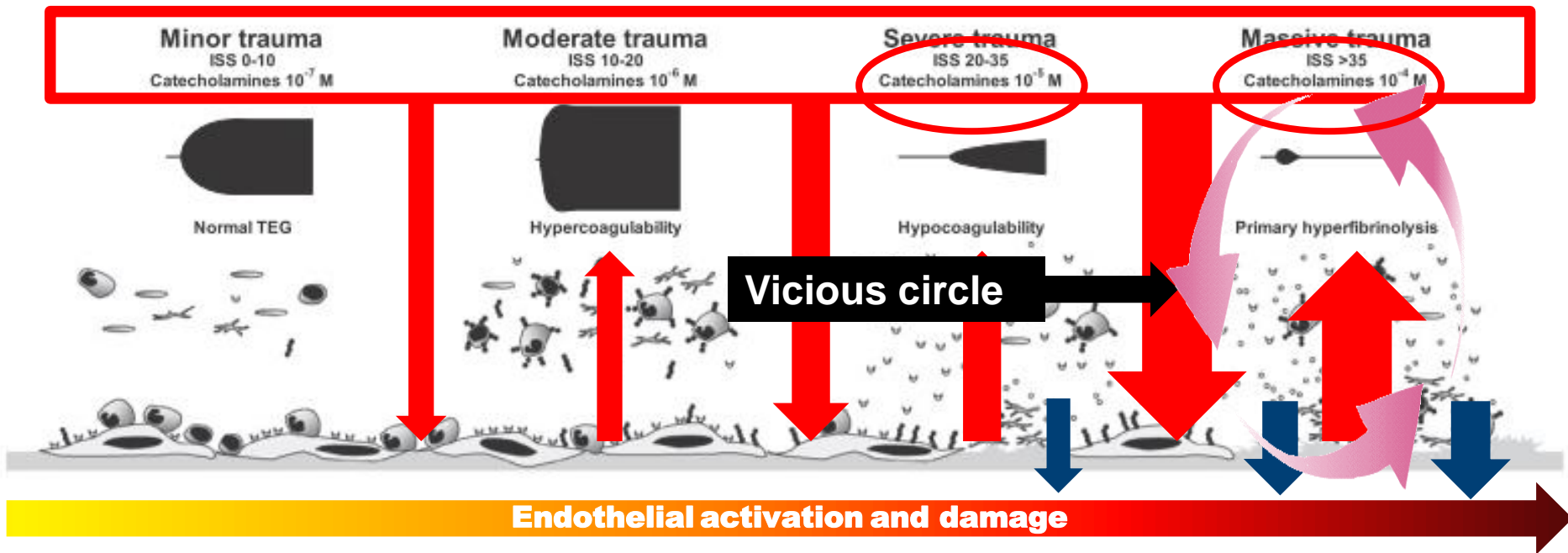
Hypocoagulability

Massive trauma
ISS >35

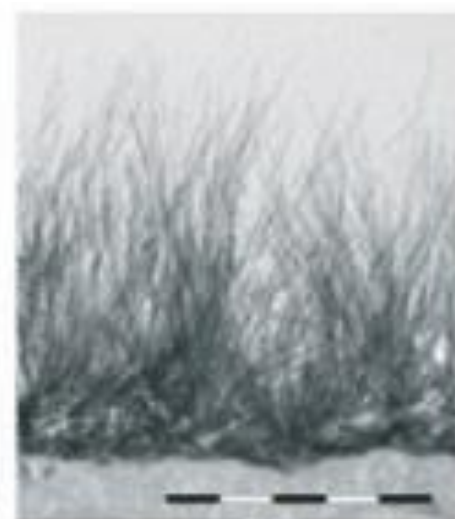
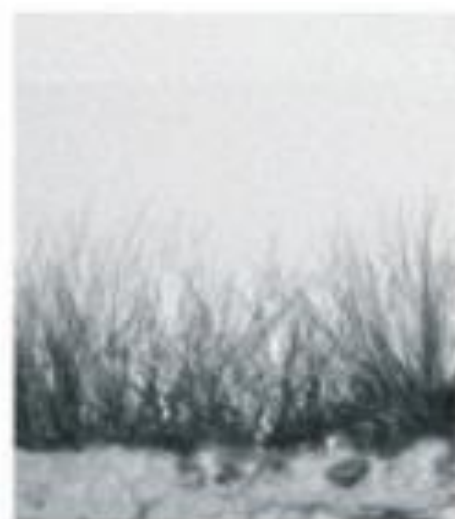
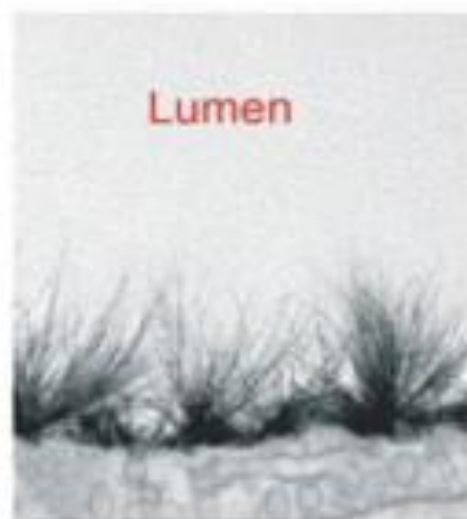
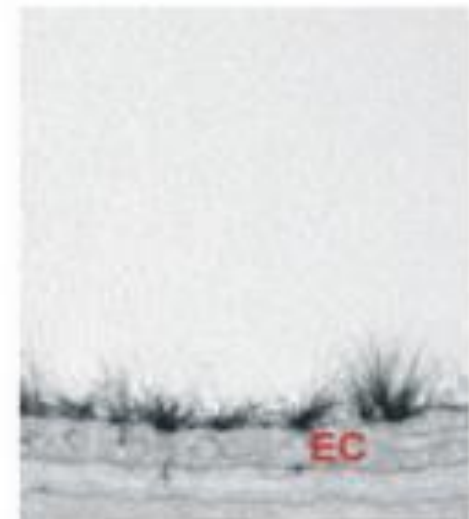
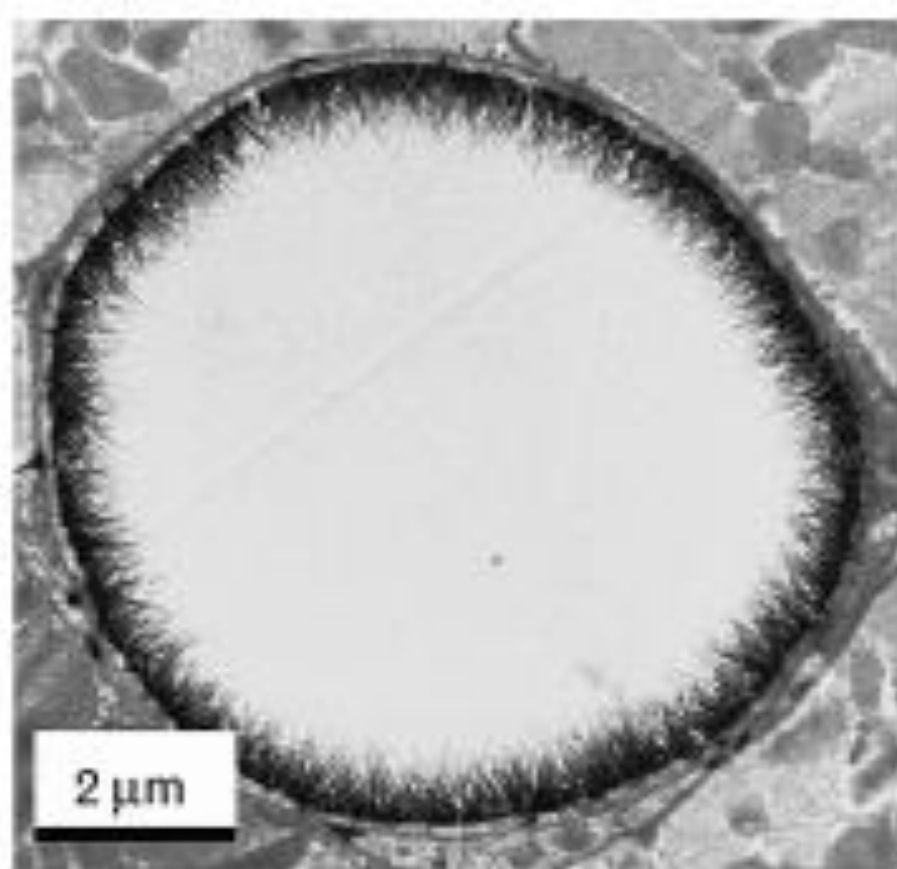
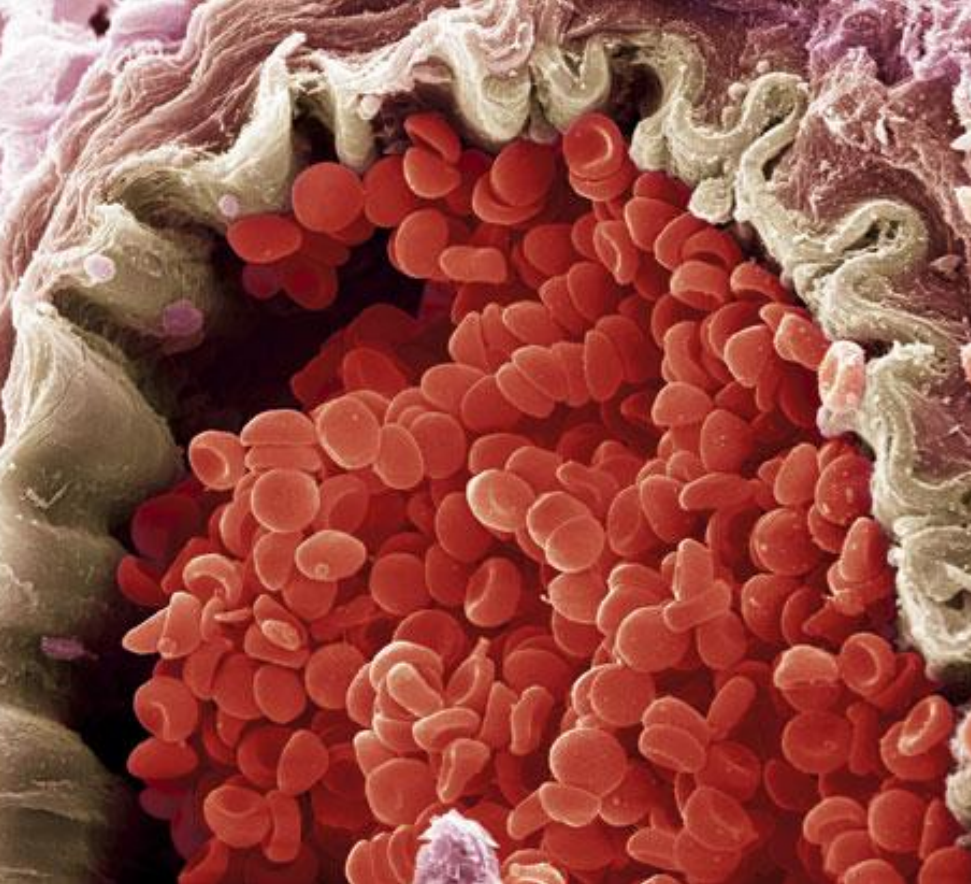


Primary hyperfibrinolysis

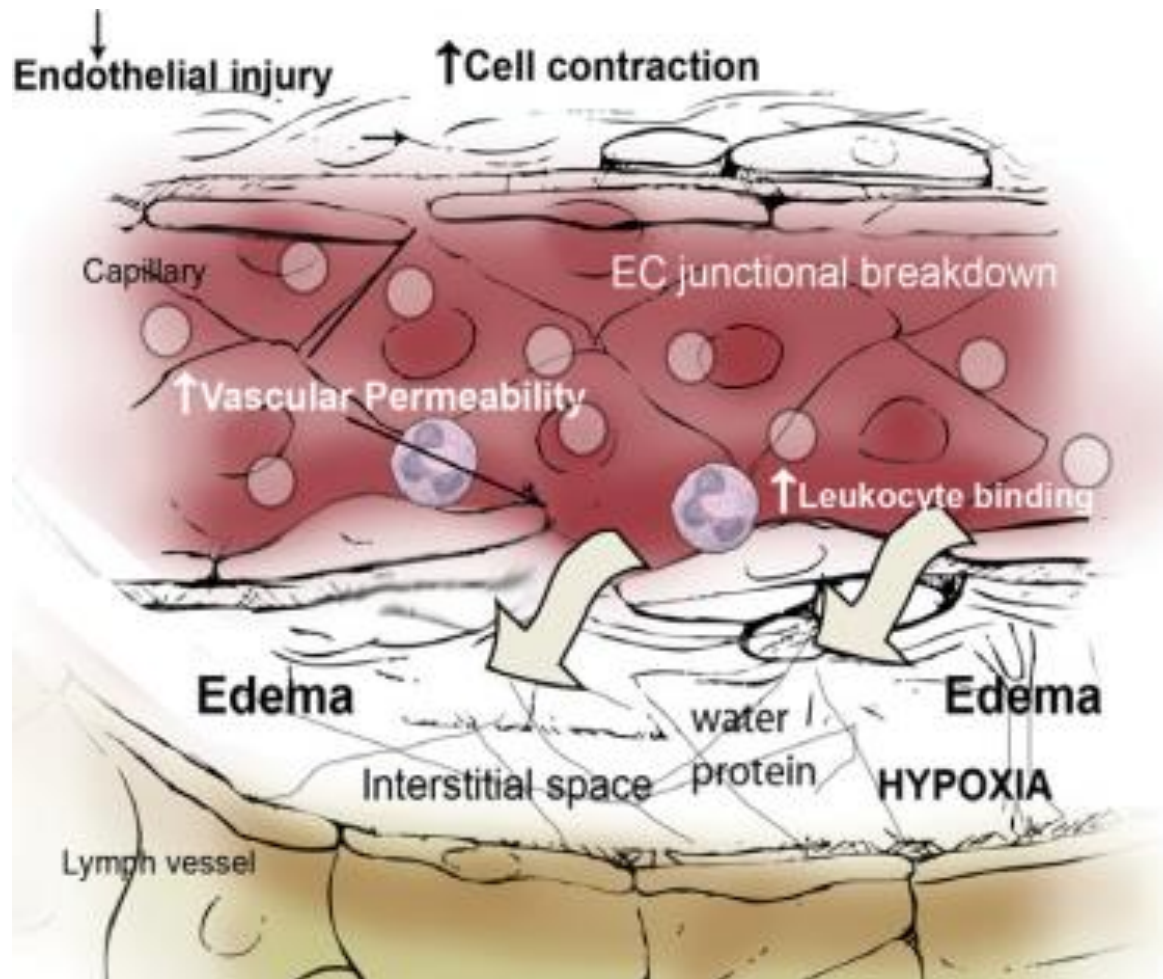
TRAUME-INDUCERET KOAGULOPATI



Oxygen versus hæmostase



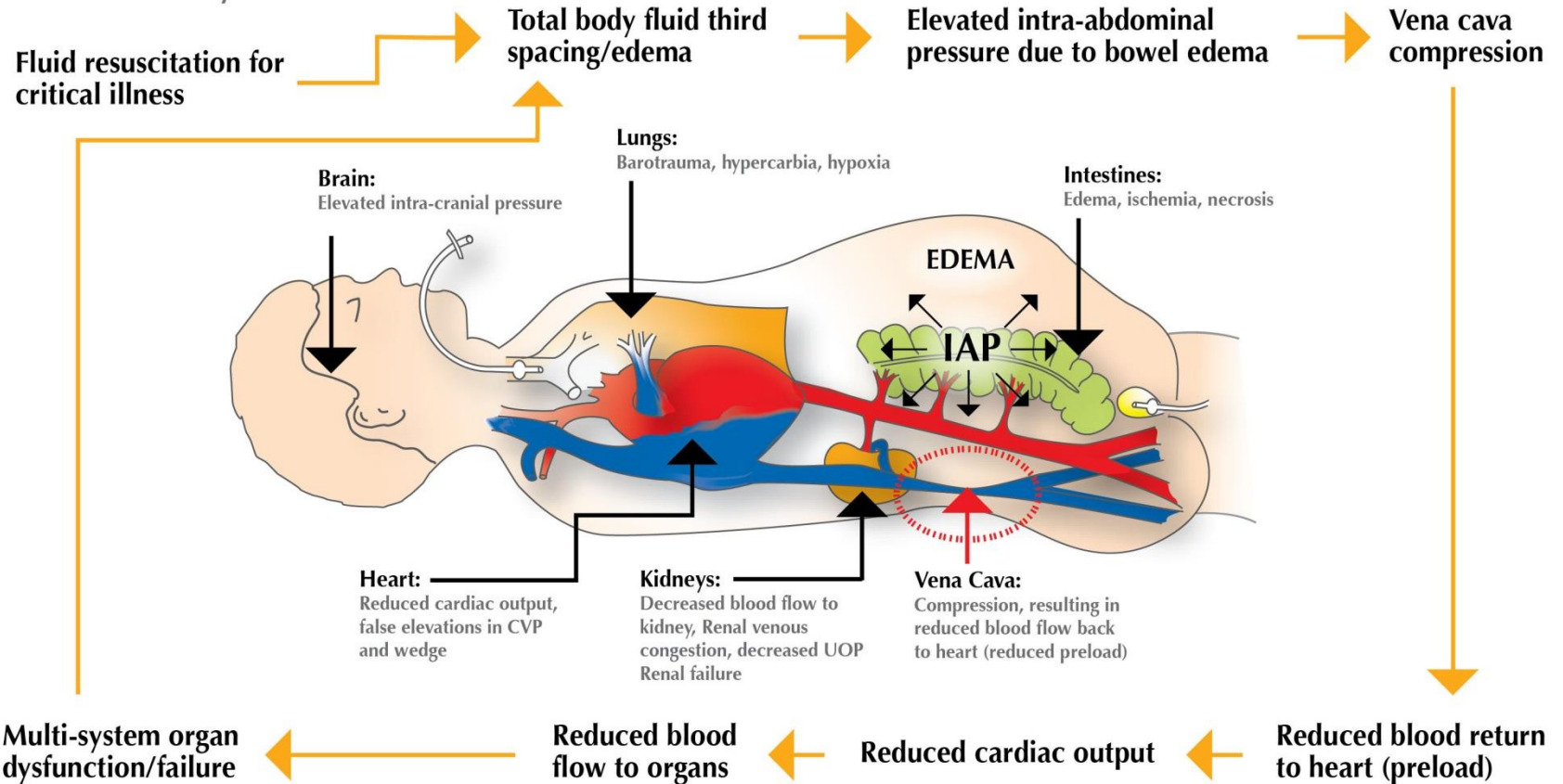
Skade på karbarriere



Kapillærlækage Syndrom

What Happens to the Body's Organs?

A Vicious Cycle



High circulating adrenaline levels at admission predict increased mortality after trauma

Pär Ingemar Johansson, MD, DMSc, MPA, Jakob Stensballe, MD, PhD,
Lars Simon Rasmussen, MD, PhD, DMSc, and Sisse Rye Ostrowski, MD, PhD, DMSc,
Copenhagen, Denmark

J Trauma
Volume 72, Number 2

TABLE 4. Univariate and Multivariate Logistic Regression Models With 30-d Mortality as Main Endpoint in Trauma Patients

	Univariate (n = 69)			Multivariate (n = 69)		
	OR (95% CI)	χ^2	<i>p</i>	OR (95% CI)	χ^2	<i>p</i>
ISS	1.1 (1.0–1.1)	10	0.001	—		
Age (yr)	1.1 (1.0–1.1)	13	<0.001	1.1 (1.0–1.2)	10	0.001
Adrenaline (ng/mL)	3.6 (1.6–8.4)	9	0.003	5.5 (1.2–26.2)	5	0.031
APTT (s)	1.1 (1.0–1.2)	8	0.005	1.1 (1.0–1.3)	5	0.026
Lactate (mmol/L)	1.7 (1.2–2.3)	11	0.001	—		
Hemoglobin (mmol/L)	0.6 (0.4–0.9)	6	0.015	—		

Odds ratios with 95% CI and *p* values are shown for all variables, with *p* values in bold for variables with *p* < 0.05. OR (95% CI) associated with one unit increase in ISS, age, adrenaline, APTT, lactate, or hemoglobin. The univariate and multivariate models are based on the same 69 patients, i.e., those with complete data.

A High Admission Syndecan-1 Level, A Marker of Endothelial Glycocalyx Degradation, Is Associated With Inflammation, Protein C Depletion, Fibrinolysis, and Increased Mortality in Trauma Patients

Pär I. Johansson, MD, DMSc, MPA, Jakob Stensballe, MD, PhD,† Lars S. Rasmussen, MD, PhD, DMSc,‡ and Sisse R. Ostrowski, MD, PhD, DMSc**

TABLE 2. Univariate and Multivariate Logistic Regression Models with 30-day Mortality as Main Endpoint in 75 Trauma Patients

	Univariate			Multivariate		
	OR (95% CI)*	χ^2	<i>P</i>	OR (95% CI) ¹	χ^2	<i>P</i>
Age (years)†	1.07 (1.03-1.11)	12	<0.001	1.09 (1.04-1.14)	12	<0.001
ISS scores‡	1.06 (1.03-1.10)	12	<0.001	1.08 (1.03-1.13)	10	0.002
Syndecan-1 (ng/mL)§	1.01 (1.01-1.02)	11	0.001	1.01 (1.00-1.02)	4	0.043

*Odds ratios with 95% confidence intervals (OR [95% CI]) and *P* values are shown, with *P* values in bold for variables with *P* < 0.05.

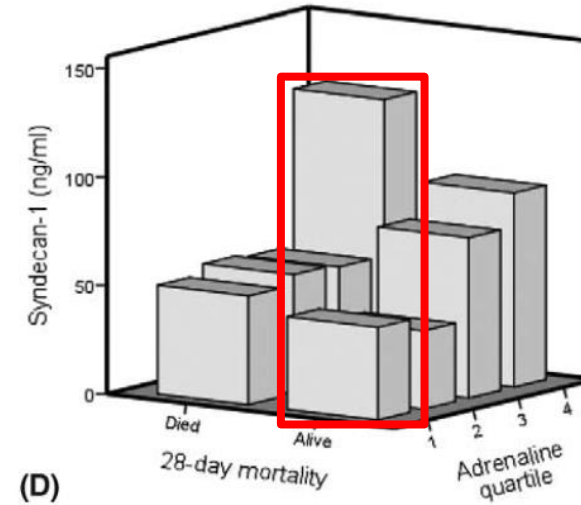
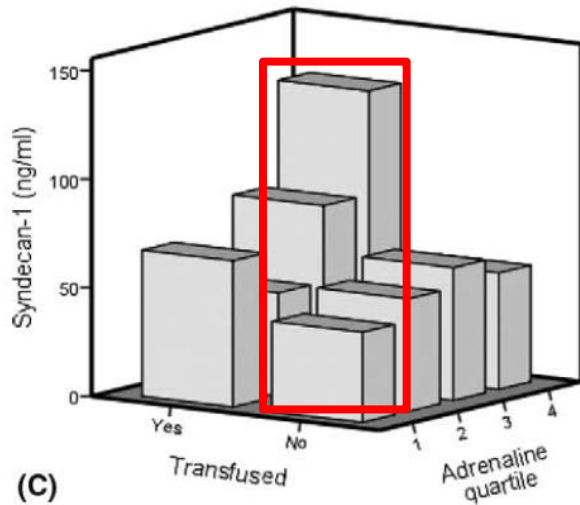
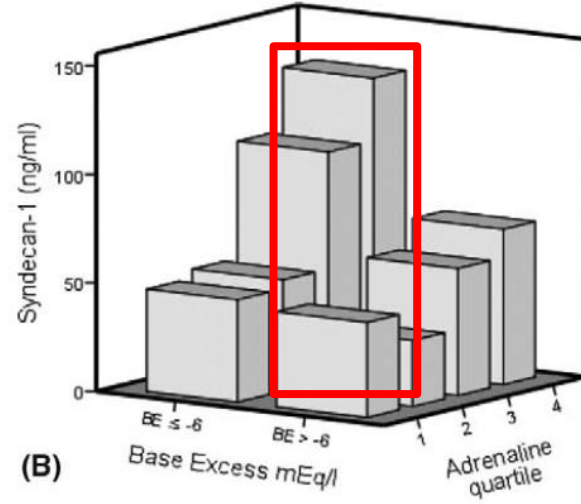
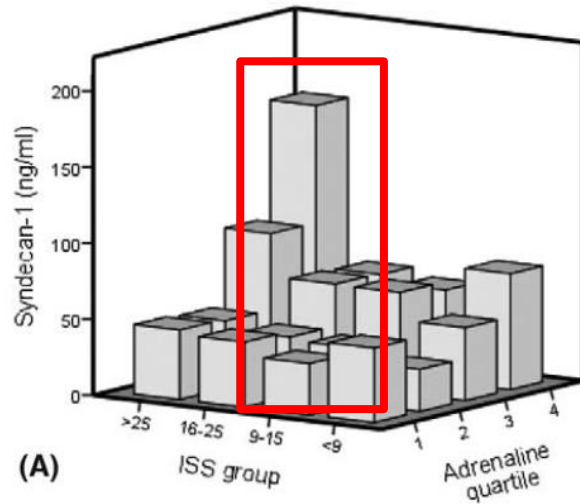
†One year older.

‡One unit increase in ISS.

§One ng/mL higher plasma concentration.

Traumatic Endotheliopathy: A Prospective Observational Study of 424 Severely Injured Patients

Pär I. Johansson, MD, DMSc, MPA,*† Hanne H. Henriksen, BSc,* Jakob Stensballe, MD, PhD,*‡
Mikkel Gybel-Brask, MD,* Jessica C. Cardenas, PhD,† Lisa A. Baer, BSc,† Bryan A. Cotton, MD, MPH,†
John B. Holcomb, MD,† Charles E. Wade, PhD,† and Sisse R. Ostrowski, MD, PhD, DMSc*



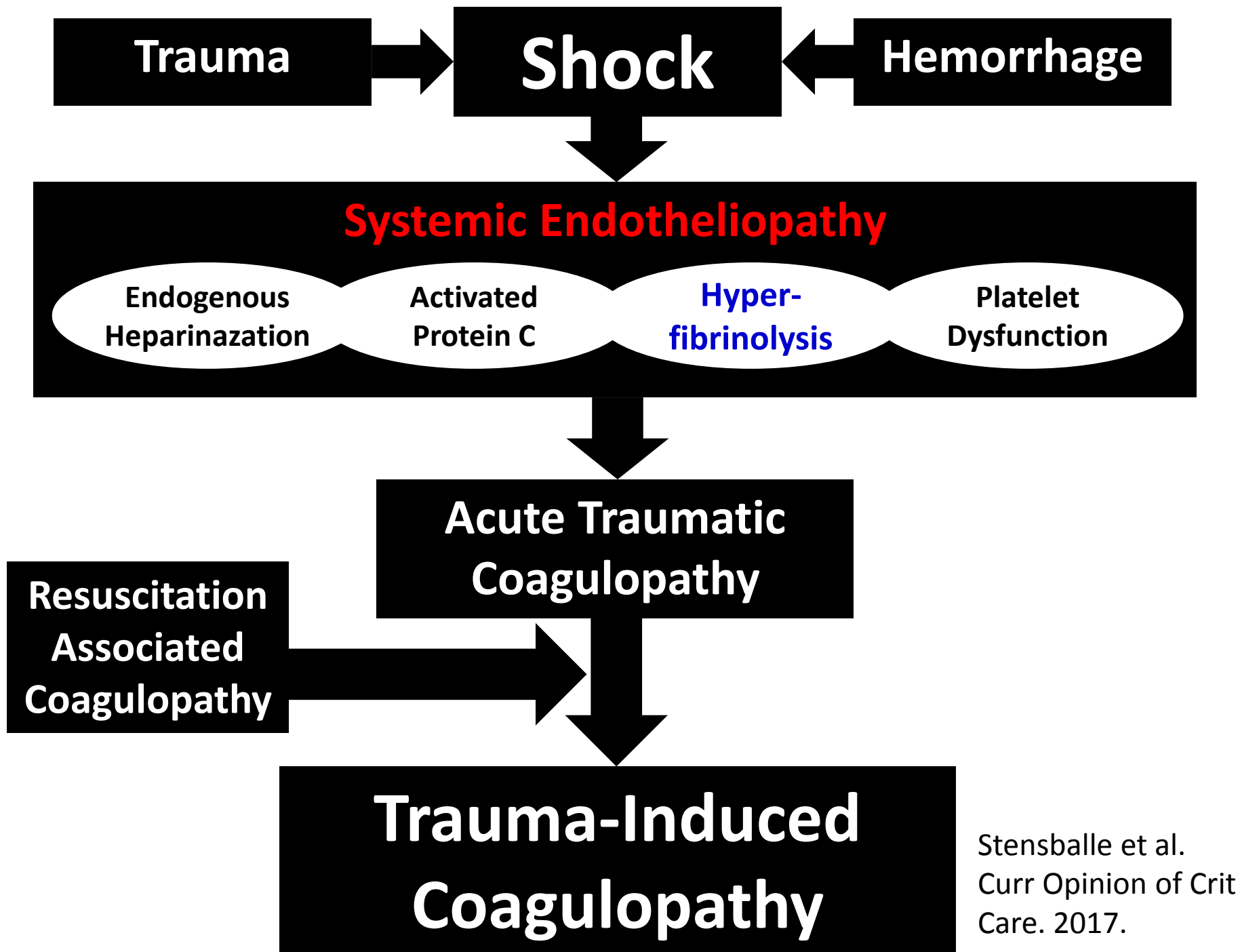
Syndecan-1: A Quantitative Marker for the Endotheliopathy of Trauma



Erika Gonzalez Rodriguez, MD, Sisse R Ostrowski, MD, DMSc, Jessica C Cardenas, PhD, Lisa A Baer, BSc, Jeffrey S Tomasek, MD, Hanne H Henriksen, BSc, Jakob Stensballe, MD, PhD, Bryan A Cotton, MD, MPH, FACS, John B Holcomb, MD, FACS, Pär I Johansson, MD, DMSc, Charles E Wade, PhD

Table 2. Blood Products and Crystalloid Use, Outcomes, and Mortality Comparisons Between Endotheliopathy of Trauma-Positive and Endotheliopathy of Trauma-Negative Patients

Variable	Total	EoT-*	EoT+†	p Value
n	410	272	138	
Transfusion				
Transfused, n (%)	198 (48.3)	99 (36.4)	99 (71.7)	<0.001
RBC, U, median (IQR)	0 (0–2)	0 (0–1)	2 (0–6)	<0.001
Plasma, U, median (IQR)	0 (0–2)	0 (0–1)	2 (0–6)	<0.001
Platelets, U, median (IQR)	0 (0)	0 (0)	0 (0–2)	<0.001
24-h total blood, ‡ U, median (IQR)	0 (0–6)	0 (0–2)	4 (0–16)	<0.001
24-h total crystalloid volume, mL, median (IQR)	1,600 (0–3,700)	0 (0–2,600)	3,100 (300–5,800)	<0.001
Outcomes				
Hospital-free days, median (IQR)	21 (4–27)	23 (10–28)	13 (0–25)	<0.001
ICU-free days, median (IQR)	28 (16–30)	28 (21–30)	23 (0–29)	<0.001
Ventilator-free days, median (IQR)	29 (20–30)	29 (26–30)	28 (0–30)	<0.001
24-h mortality, n (%)	39 (9.5)	16 (5.9)	23 (16.7)	0.001
30-d in-hospital mortality, n (%)	67 (16.3)	33 (12.1)	34 (24.6)	0.001

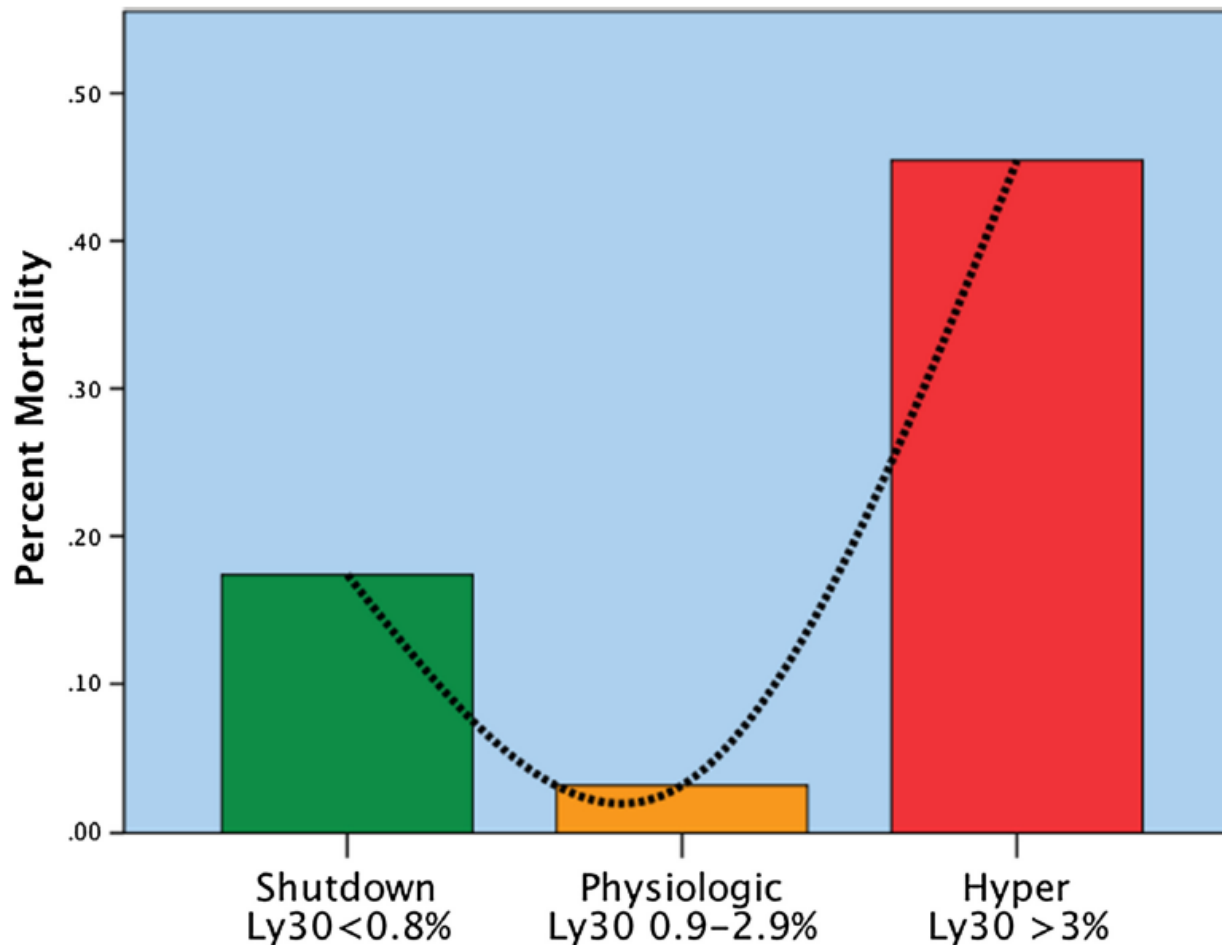


Stensballe et al.
Curr Opin of Crit
Care. 2017.

Hyperfibrinolysis, physiologic fibrinolysis, and fibrinolysis shutdown: The spectrum of postinjury fibrinolysis and relevance to antifibrinolytic therapy

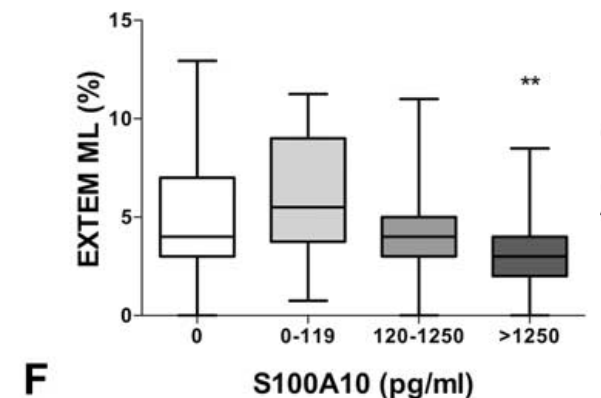
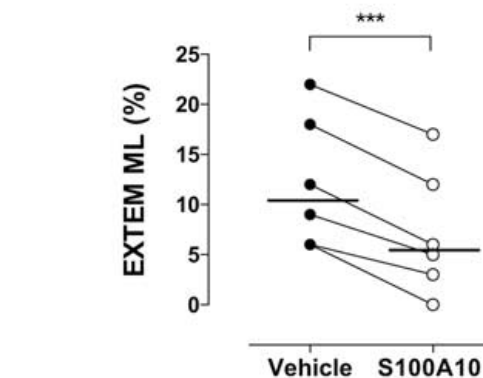
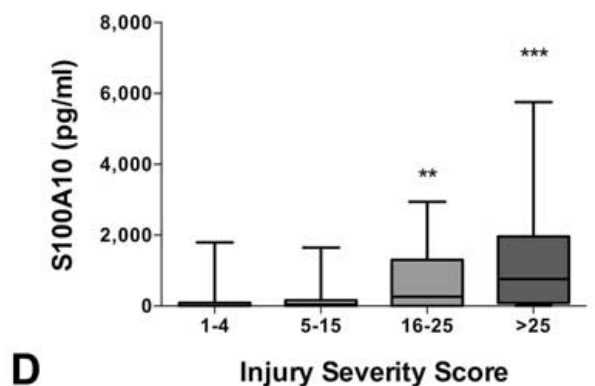
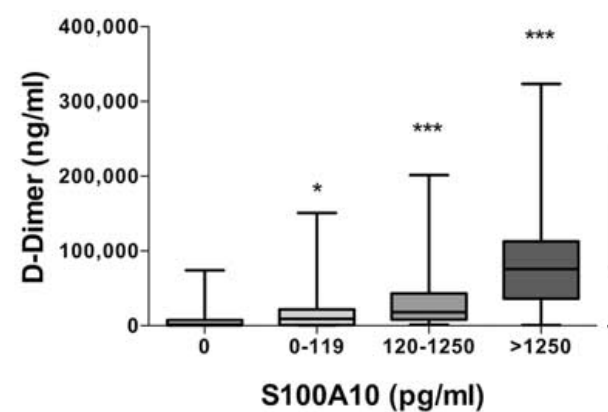
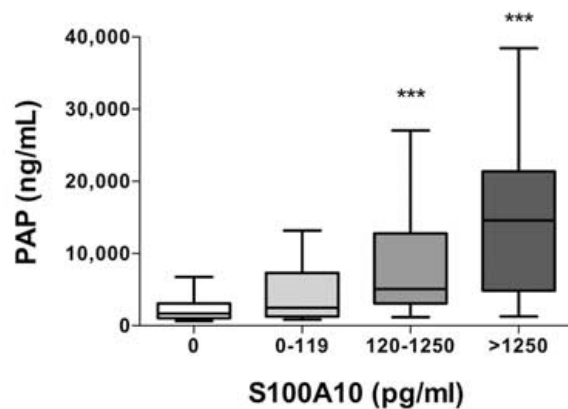
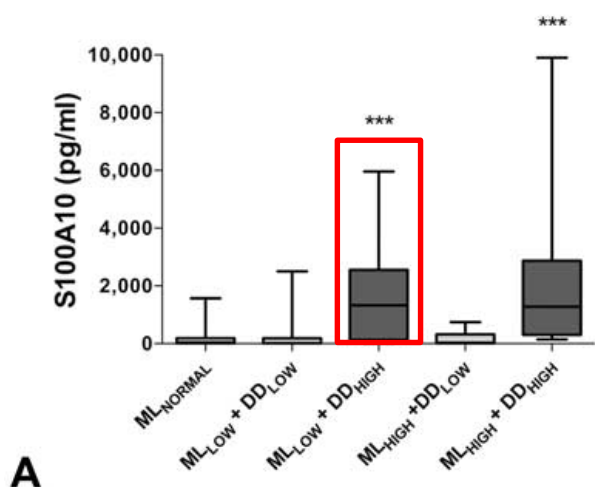
Hunter B. Moore, MD, Ernest E. Moore, MD, Eduardo Gonzalez, MD, Michael P. Chapman, MD, Theresa L. Chin, MD, Christopher C. Silliman, MD, PhD, Anirban Banerjee, PhD, and Angela Sauaia, MD, PhD, *Denver, Colorado*

J Trauma Acute Care Surg 2014



The S100A10 Pathway Mediates an Occult Hyperfibrinolytic Subtype in Trauma Patients

Lewis S. Gall, MD,* Paul Vulliamy, MD,* Scarlett Gillespie, PhD,* Timothy F. Jones, MD,*
 Rochelle S. J. Pierre,* Sabine E. Breukers,* Christine Gaarder, MD, PhD,† Nicole P. Juffermans, MD, PhD,‡
 Marc Maegele, MD,§ Jakob Stensballe, MD,¶||** Pär I. Johansson, MD, DMSc, MPA,¶||**
 Ross A. Davenport, MD, PhD,* and Karim Brohi, MD*, Targeted Action for Curing Trauma-Induced
 Coagulopathy (TACTIC) partners
Ann Surg 2018



A Novel and Potentially Unifying Mechanism for Shock Induced Early Coagulopathy

John B. Holcomb, MD, FACS*

Dr. Johansson and colleagues have published a novel and potentially unifying mechanism for shock induced early coagulopathy. The interplay between catecholamines, endothelial dysfunction, inflammation and coagulation is exciting and thought provoking. However, caution is required, because as the authors state, their findings are only associations revealed in a small study of 2700 patients and their data serve to provide hypotheses.

The authors have largely focused their attention on the glycocalyx, which consists of proteoglycans and glycoproteins attached to a syndecan backbone, which together protect the underlying endothelium. Syndecan-1 is one of the major constituents of the glycocalyx. The glycocalyx not only reacts to intravascular insults, but when enzymatically shed, serves as a mediator of transduction of these insults to the endothelial cell. Reim described glycocalyx shedding in elective aortic surgery, with different syndecan levels before and after aortic clamping.⁶ Dr. Johansson found similar results in trauma patients and has offered several novel therapeutic approaches for improved outcomes.

These are exciting areas of investigation and have largely focused on endothelial barrier function in response to the systemic biological stimulus of hemorrhagic shock.

- Basic science efforts have been focused on the endothelial response to shock, specifically endothelial permeability, intracellular dysfunction and edema.
- Childs has reported that to induce intracellular microvascular permeability occurs mainly because of the disruption of the glycocalyx.⁷
- Cohen and Brohi have reported that the Acute Coagulopathy of Trauma Shock (ACoTS) is caused by a combination of tissue injury, endothelial damage and shock, may occur without significant fluid administration, clotting factor depletion or hypothermia and the resuscitation of the protein C pathway may improve the clinical outcome.⁸
- Resuscitation with fresh frozen plasma (FFP) is associated with improved outcome after severe hemorrhagic shock. FFP has protective and stabilizing effects on coagulation, endothelial cell (EC) permeability, improved vascular stability and improved resuscitation in vivo after HS.
- Many authors have shown that autoresuscitation (increased blood pressure without fluid infusion) occurs after hemorrhage, based on increased endothelial permeability and translocation of fluid from the extravascular to intravascular space. Uncontrolled versus controlled hemorrhage animal studies exhibit very different physiologic responses, for example uncontrolled hemorrhage models have drops in blood pressure out of proportion to blood loss.⁹ Many feel that this response is neutrally mediated and is protective, serving to decrease blood loss. These adaptive evolutionary responses are the result of the autonomic response to resuscitation, either the hypoxic, crystalloid resuscitation, or the hyperosmolar resuscitation and in the case of the latter, the hyperosmolar resuscitation.¹⁰ Trauma patients who are resuscitated with normal saline have been shown to have increased endothelial permeability, increased intracellular dysfunction and increased intracellular edema.¹¹ Recently reported that stimulation of the vagus nerve increases enteric glia activation, which is associated with improved intestinal barrier function.^{12,18}

Trauma

N ≈ 2700 patients

Severe infection including sepsis

N ≈ 1800 patients

Acute myocardial infarction

N ≈ 700 patients

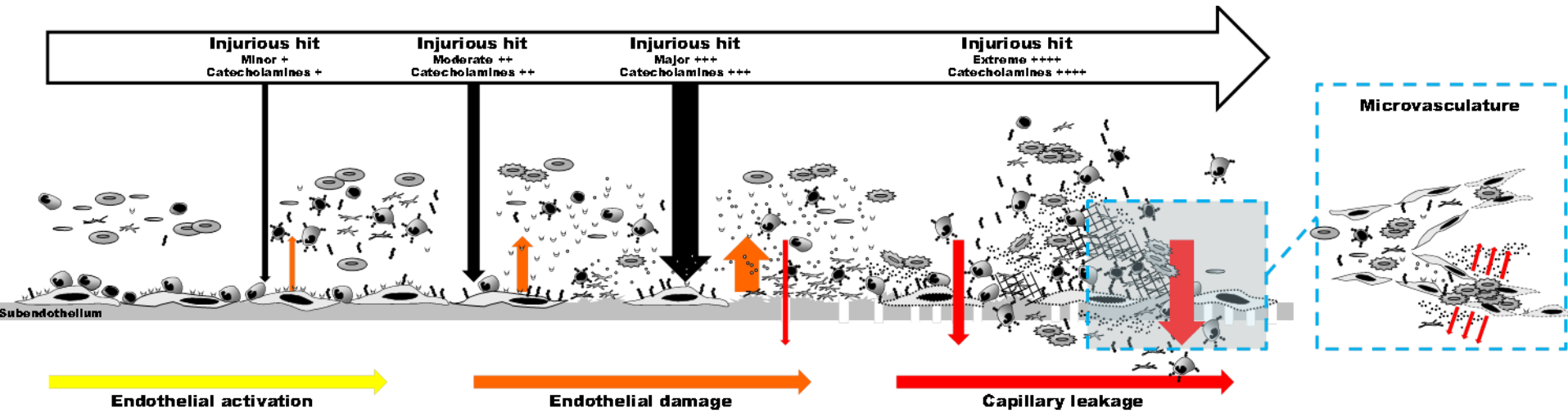
Resuscitated cardiac arrest

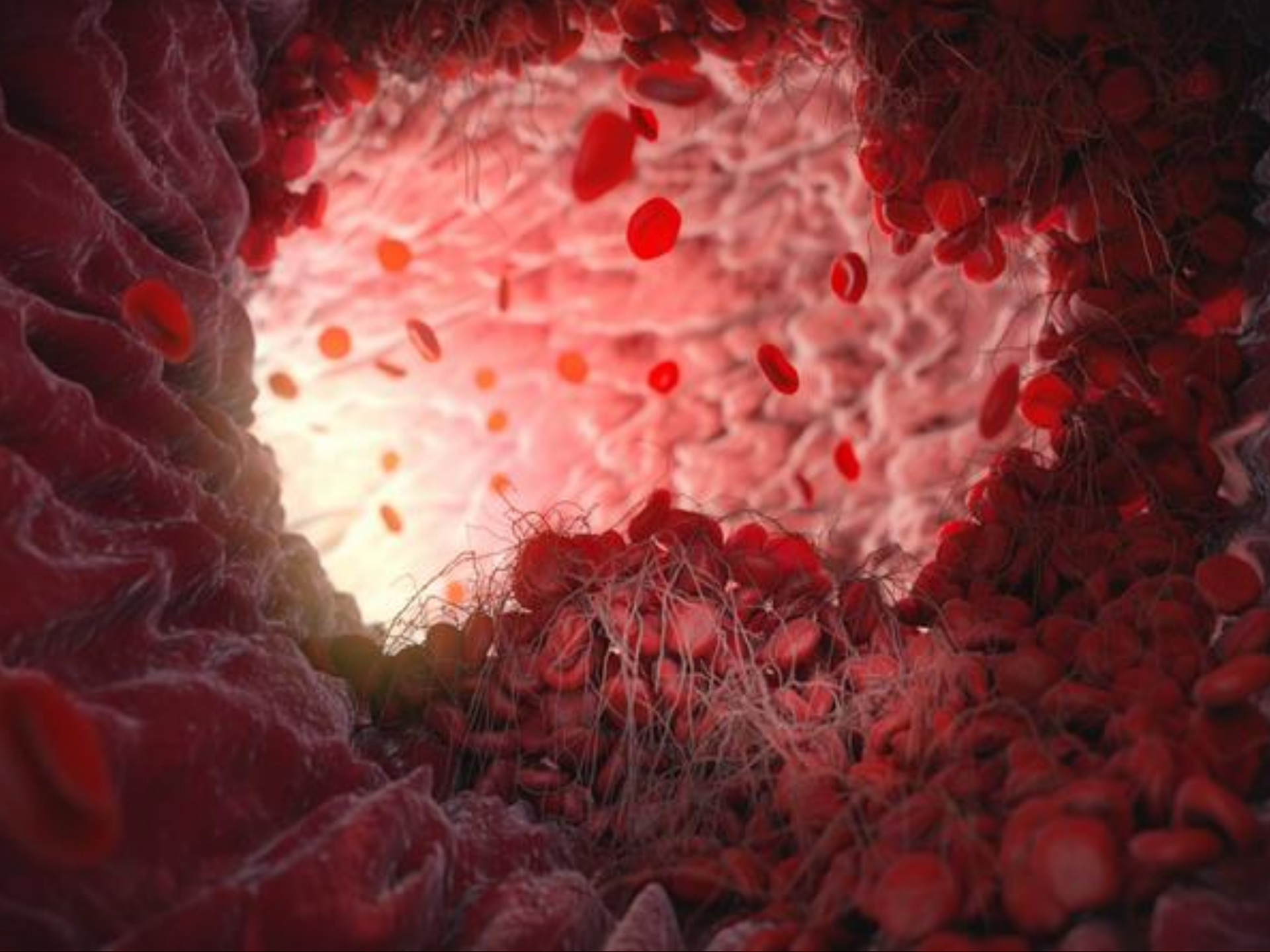
N ≈ 160 patients

Akut Kritisk Syge patienter udviser samme unike type endotheliopati som øger dødeligheden

SHock-INDuced Endotheliopathy

SHINE





Trauma

Shock

Hemorrhage

Systemic Endotheliopathy

Endogenous
Heparinization

Activated
Protein C

Hyper-
fibrinolysis

Platelet
Dysfunction

**Acute Traumatic
Coagulopathy**

**Resuscitation
Associated
Coagulopathy**

**Trauma-Induced
Coagulopathy**

Stensballe et al.
Curr Opin of Crit
Care. 2017

Livstruende blødning

1:1:1
3:3:1-4:4:2

Akut transfusionspakke

Indhold

1.55L

2

3

Clear Trombo

es straks!

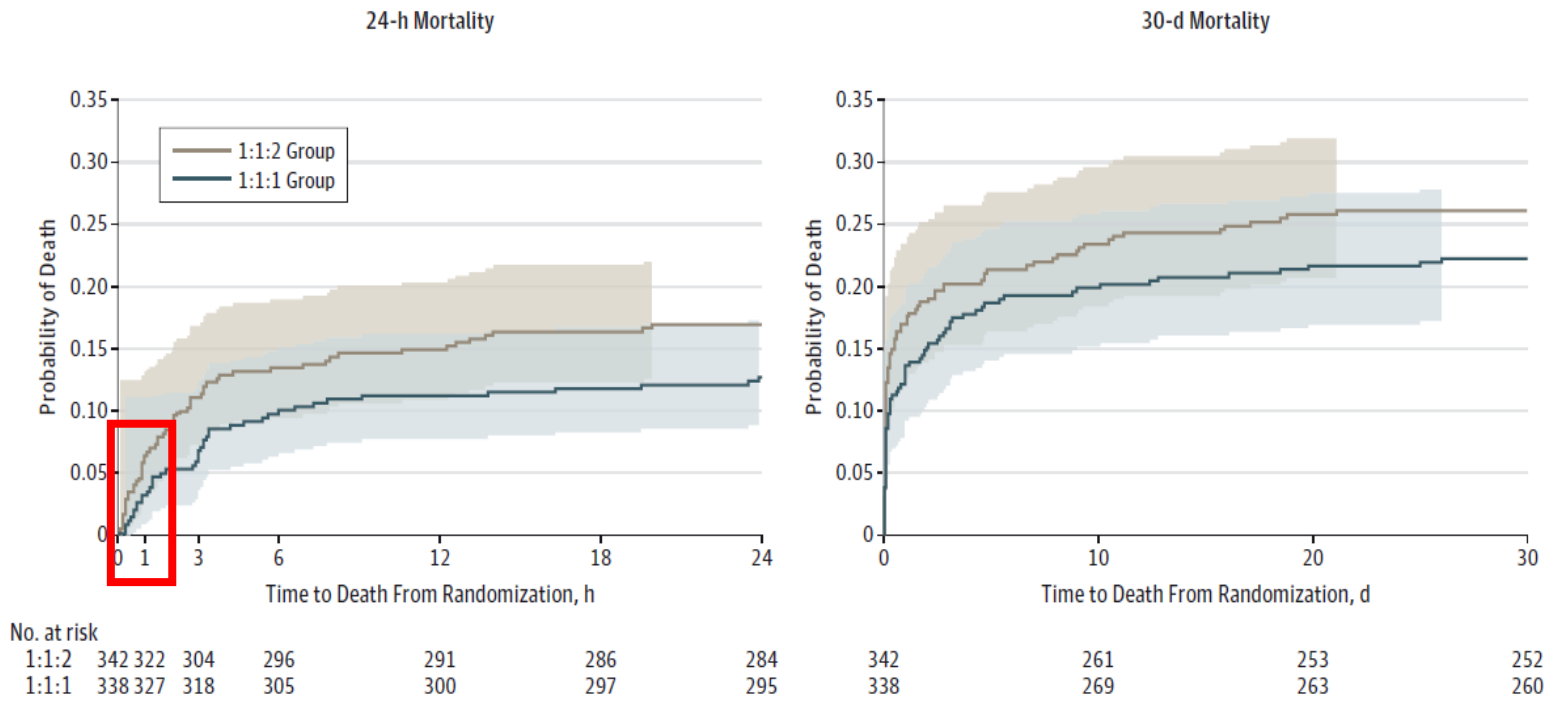
10 13:32

The Belmont Rapid Infuser

An: 2044

Transfusion of Plasma, Platelets, and Red Blood Cells in a 1:1:1 vs a 1:1:2 Ratio and Mortality in Patients With Severe Trauma The PROPPR Randomized Clinical Trial

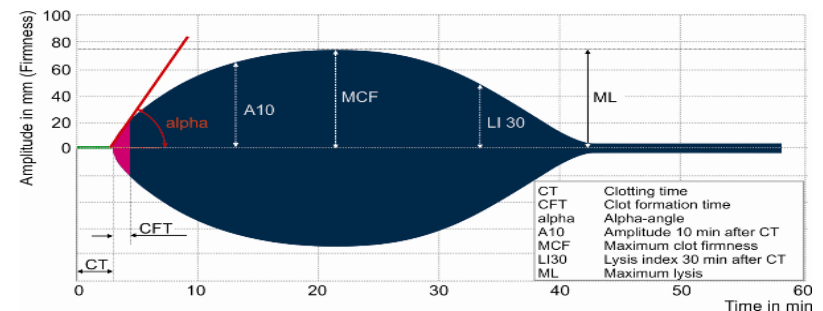
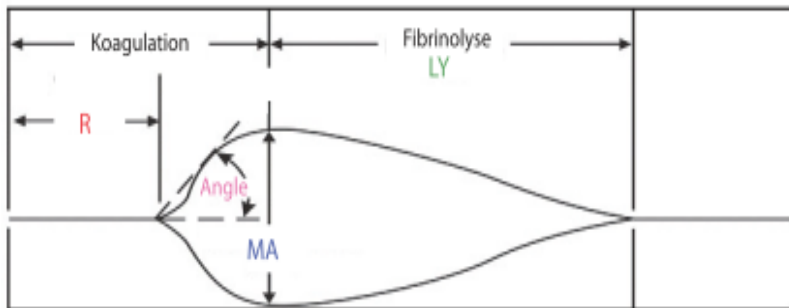
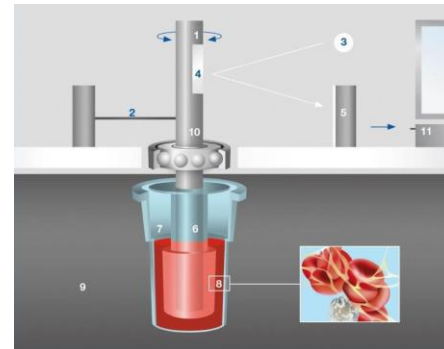
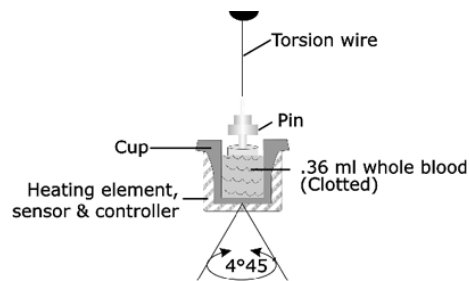
Figure 2. Kaplan-Meier Failure Curves for Mortality at 24 Hours and 30 Days



Viscoelastic Haemostatic Assays (VHA)

TEG[®]/ROTEM[®]

- Whole blood analysis
- Measures the viscoelastic properties of the clot
- Multiple endpoints reflecting clot formation, strength & degradation
- Real-time (15 min.)



Thromboelastography (TEG) or thromboelastometry (ROTEM) to monitor haemostatic treatment versus usual care in adults or children with bleeding (Review)



Cochrane
Library

Cochrane Database of Systematic Reviews

Wikkelsø A, Wetterslev J, Møller AM, Afshari A

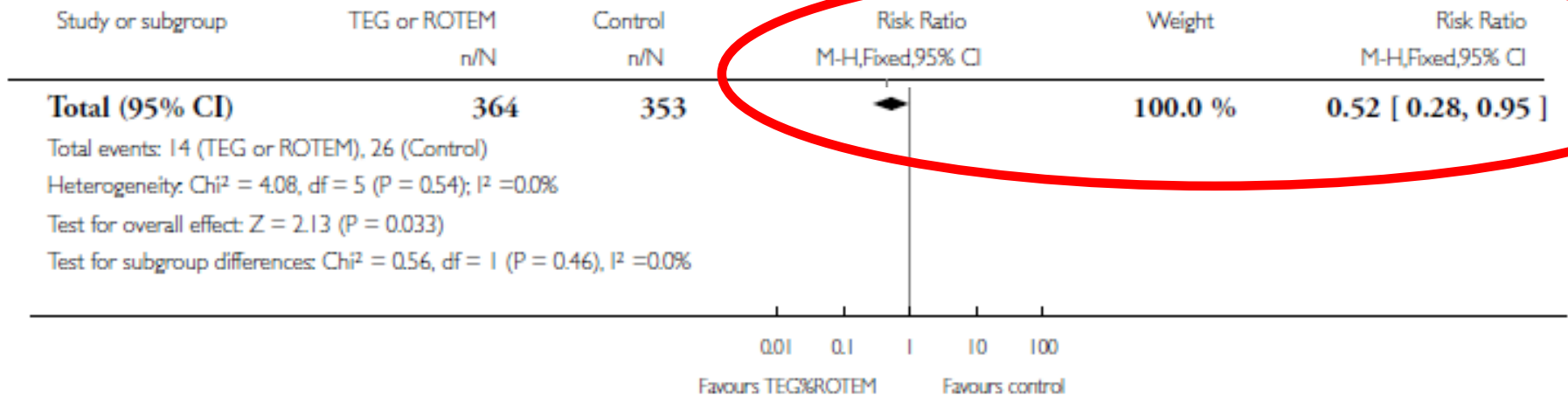
Cochrane Database of Systematic Reviews 2016, Issue 8. Art. No.: CD007871.

Analysis 1.1. Comparison 1 TEG or ROTEM versus any comparison, Outcome 1 Mortality; grouped by TEG or ROTEM.

Review: Thromboelastography (TEG) or thromboelastometry (ROTEM) to monitor haemostatic treatment versus usual care in adults or children with bleeding

Comparison: 1 TEG or ROTEM versus any comparison

Outcome: 1 Mortality; grouped by TEG or ROTEM



Start of bleeding

Control of bleeding

Trauma-Induced-Coagulopathy

TXA 1 g IV bolus & 1 g IV in 8 hours

VHA monitoring → Goal-directed therapy with
Plasma, PLT, change of ratio, Cryo, fibrinogen & TXA

Ratio 1:1:1 (RBC, plasma, PLT)

Risk of coagulopathy
Arrival → during resuscitation & surgery

Time

VTE
prophylaxis

24. MAJ 2018

DSTH FORÅRSMØDE

AALBORG KONGRES- OG KULTURCENTER | 9000 AALBORG



TRAUME-INDUCERET KOAGULOPATI

1. Øger dødeligheden, ses hos 30-40%!
2. Aggressiv monitorering & behandling!!
3. Udløses af systemisk endotheliopati (**SHINE**), og fremtidens resuscitation vil fokuserer på genskabelse af normal endothelfunktion