

„Blut ist ein ganz besonderer Saft.“
Faust. Der Tragödie erster Teil, 1808.

J.W. Goethe (* 1749; † 1832) | Deutscher Dichter

Gerinnung in extremis

Hypothermie & Azidose
Trauma & Hämodilution
ECMO

Priv.-Doz. Dr. Benedikt Tremml, MBA

Zugehörigkeit

Ärztlicher Leiter Allgemeine & Chirurgische Intensivstation

Univ.-Klinik für Anästhesie und Intensivmedizin Innsbruck

Beauftragter für innerklinische Notfallmedizin LKI | NAH Martin 2

Interessenskonflikte

Vortragshonorare AOP Orphan, Fresenius

Reisespesen AOP Orphan, Pfizer

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01 Hypothermie & Azidose

Kalt und sauer ist nur bei Cola gut

02 Trauma & Hämodilution

Lethal triad of death and plenty of water

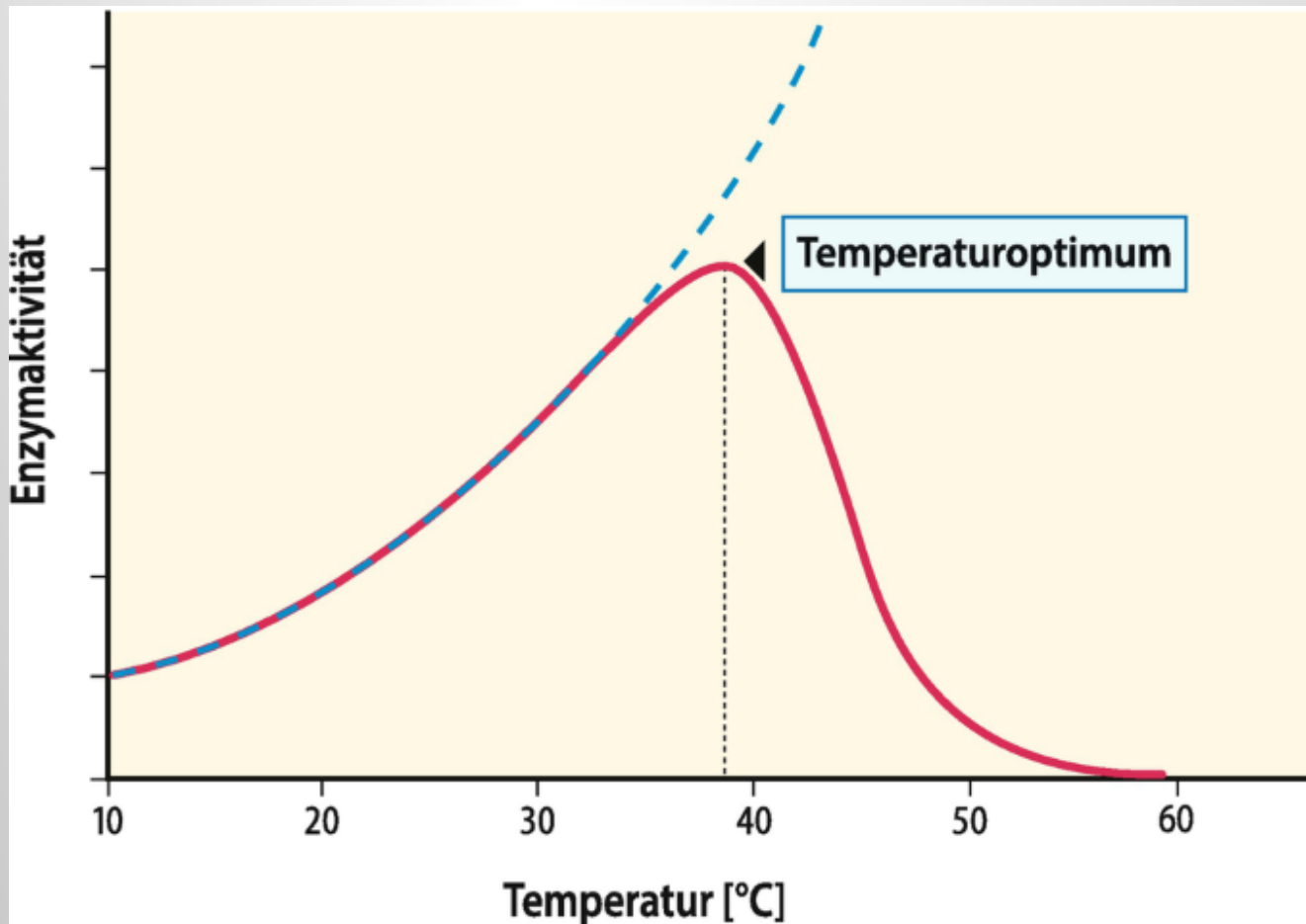
03 Sonderfall ECMO

Wenn es blutet und gerinnt gleichzeitig

04 Conclusio

Zusammenfassung

Hypothermie und Koagulopathie



- 10% ↓ of enzyme function per °C ↓¹⁻⁴
- Platelet function is impaired by temperature^{2,3}
- Fibrinolysis plays minor role in coagulopathy^{3,4}

- 1 Kriegel T et al. 2022. Regulation der Enzymaktivität. In: Heinrich, P.C., Müller, M., Graeve, L., Koch, HG. (eds) Löffler/Petrides Biochemie und Pathobiochemie. Springer, Berlin, Heidelberg.
- 2 Reed R et al. Circ. 1990. Shock. Hypothermia and blood coagulation: Dissociation between enzyme activity and clotting factor levels. 32:141–152.
- 3 Watts D et al. 1998. J Trauma. Hypothermic coagulopathy in trauma: Effect of varying levels of hypothermia on enzyme speed, platelet function, and fibrinolytic activity. 44:846–854.
- 4 Reed R. 1992. J Trauma. The disparity between hypothermic coagulopathy and clotting studies. 33:465–470.

Platelet dysfunction in hypothermia

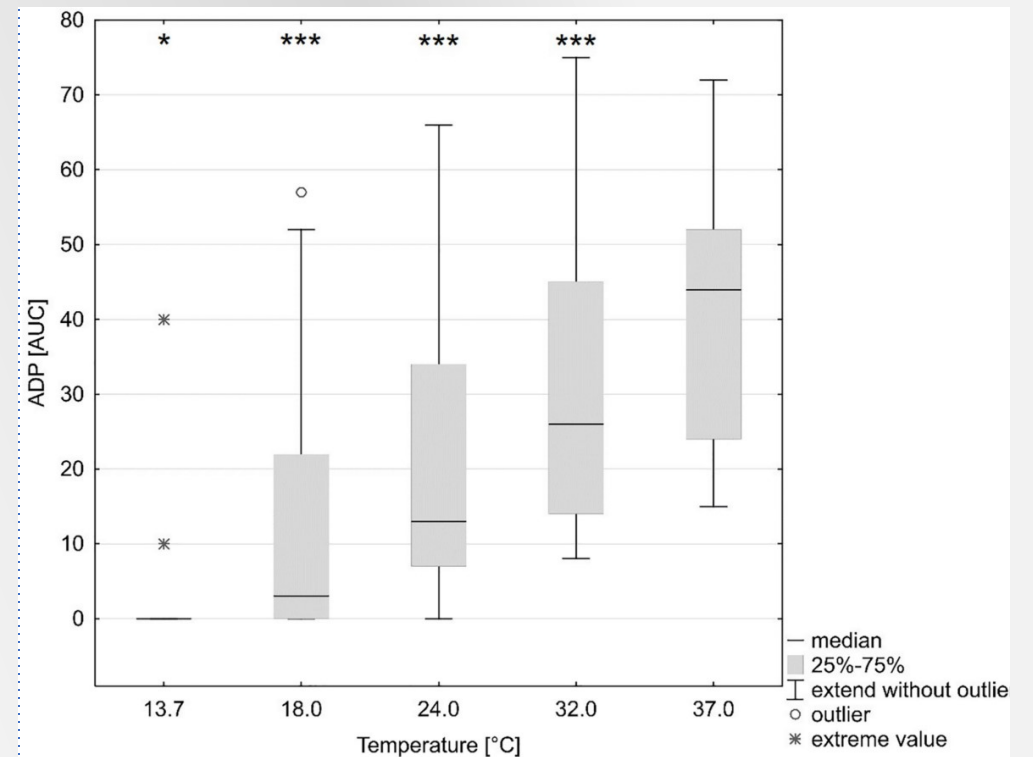
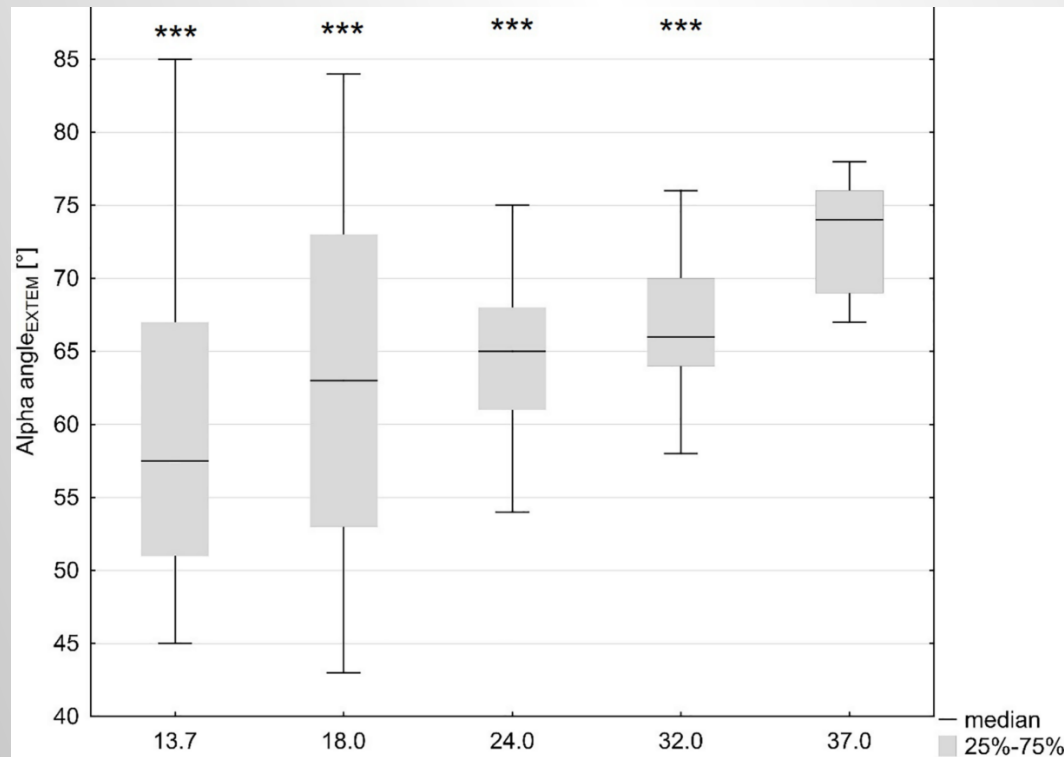
Thrombin plays a major role through a platelet adhesion defect ^{1,2}

Coupling between platelet adhesion and activation is lost between 30°C and 34°C ³

1 Wolberg A et al. 2004. J Trauma. A systematic evaluation of the effect of temperature on coagulation enzyme activity and platelet function. 56:1221–1228.

2 Wallner B et al. 2020. Front Physiol. Hypothermia-Associated Coagulopathy: A Comparison of Viscoelastic Monitoring, Platelet Function, and Real Time Live Confocal Microscopy at Low Blood Temperatures, an in vitro Experimental Study. 11:843.

3 Murphy M et al. 2017. Practical Transfusion Medicine. 5th edn. Hoboken, NJ: John Wiley and Sons.



Realität vs. Labor

in vivo vs. in vitro

Therapeutisches Ziel
>34°C

The lower the blood temperature, the more significant effect on blood coagulation decline.

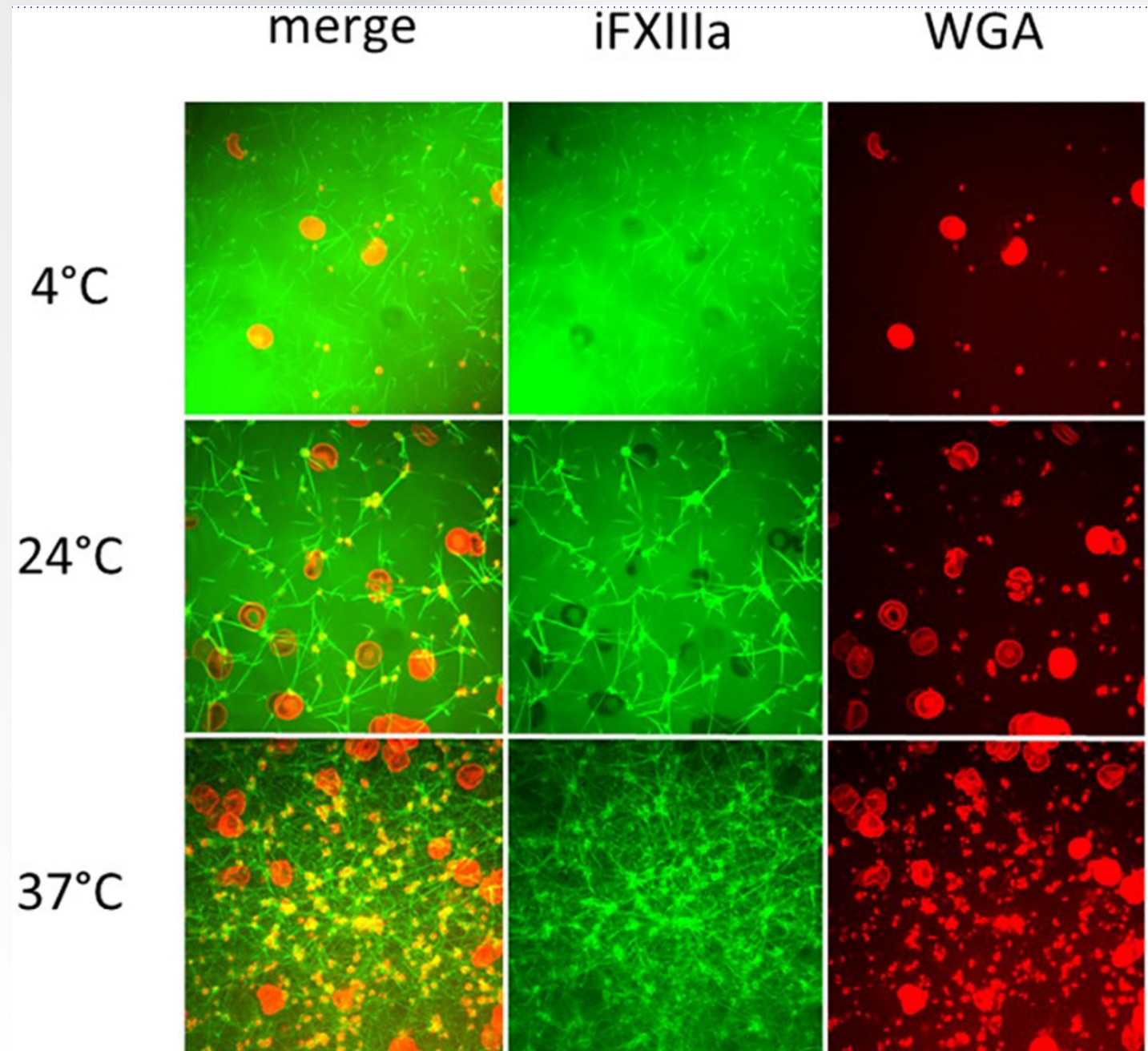
Ruzicka J et al. 2012. Blood Coagul Fibrinolysis. Hypothermic anticoagulation: testing individual responses to graded severe hypothermia with thromboelastography. 23(4):285-9.

Confocal Microscopy ¹

Fibrin: grün, FXIIIa-sensitive near-
infrared fluorescence imaging agent
RBC: rot, wheat germ agglutinin-alexa
fluor 555
PLT: gelb, WGA and iFXIIIa overlay ²

¹ Norman K. 2005. Sci Trends Pharmacol. Techniques: Intravital
microscopy—a method for investigating disseminated intravascular
coagulation? Sci.26327–263332.

² Wallner B et al. 2020. Front Physiol. Hypothermia-Associated
Coagulopathy: A Comparison of Viscoelastic Monitoring, Platelet
Function, and Real Time Live Confocal Microscopy at Low Blood
Temperatures, an in vitro Experimental Study. 11:843.



Effekte von Azidose

6+6 Schweine mit pH 7.1¹

⇒ MAP, HCO₃⁻, BE ↓

⇒ Fibrinogen, PLT ↓

⇒ Fibrinogendegradation ↑

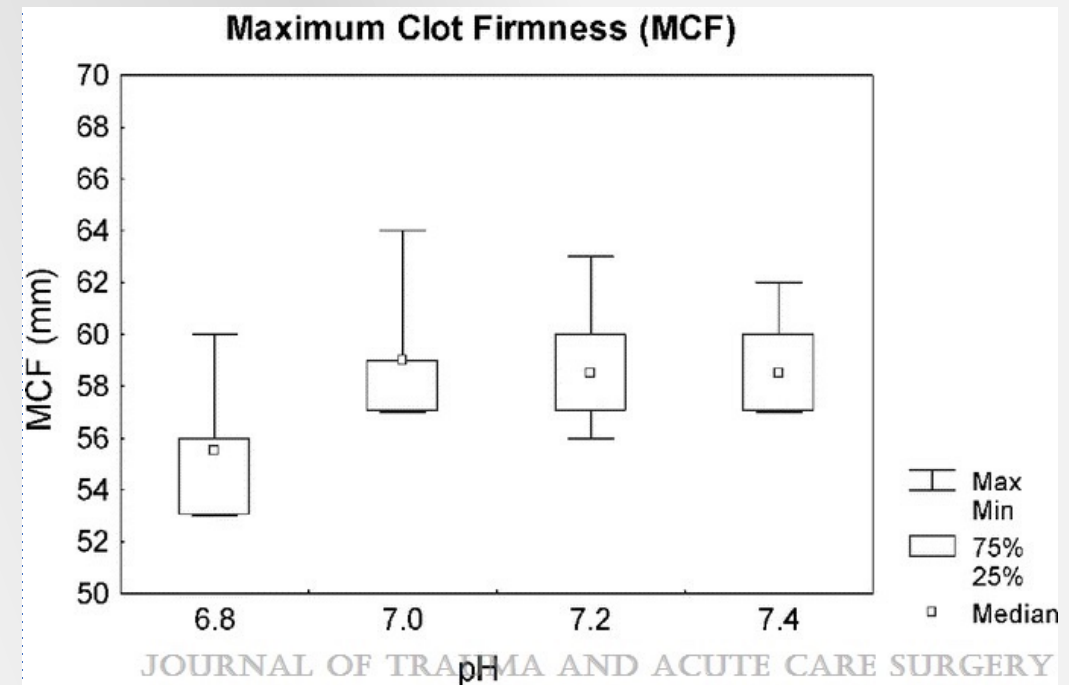
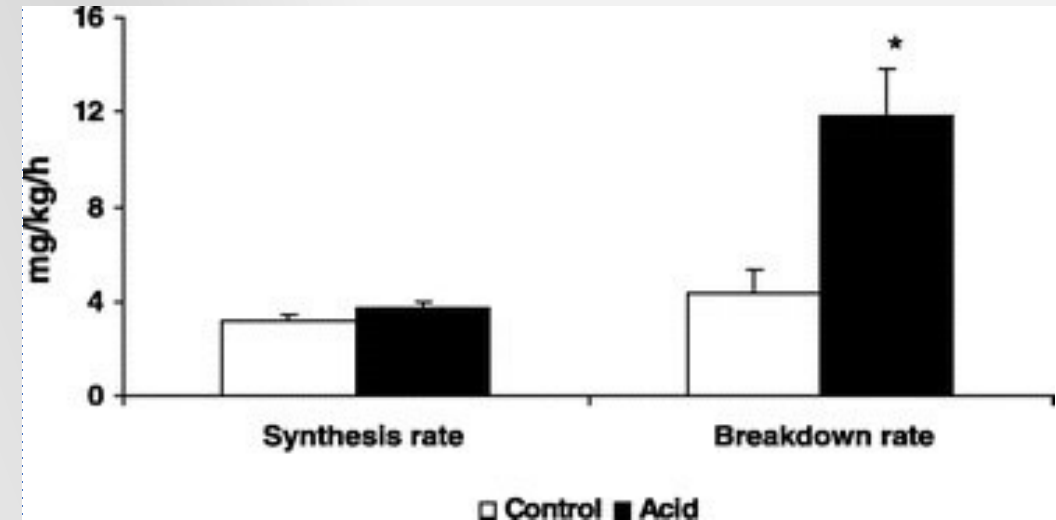
⇒ PT, aPTT, ACT ↑

ROTEM: α-Winkel und Gerinnselfestigkeit² ↓

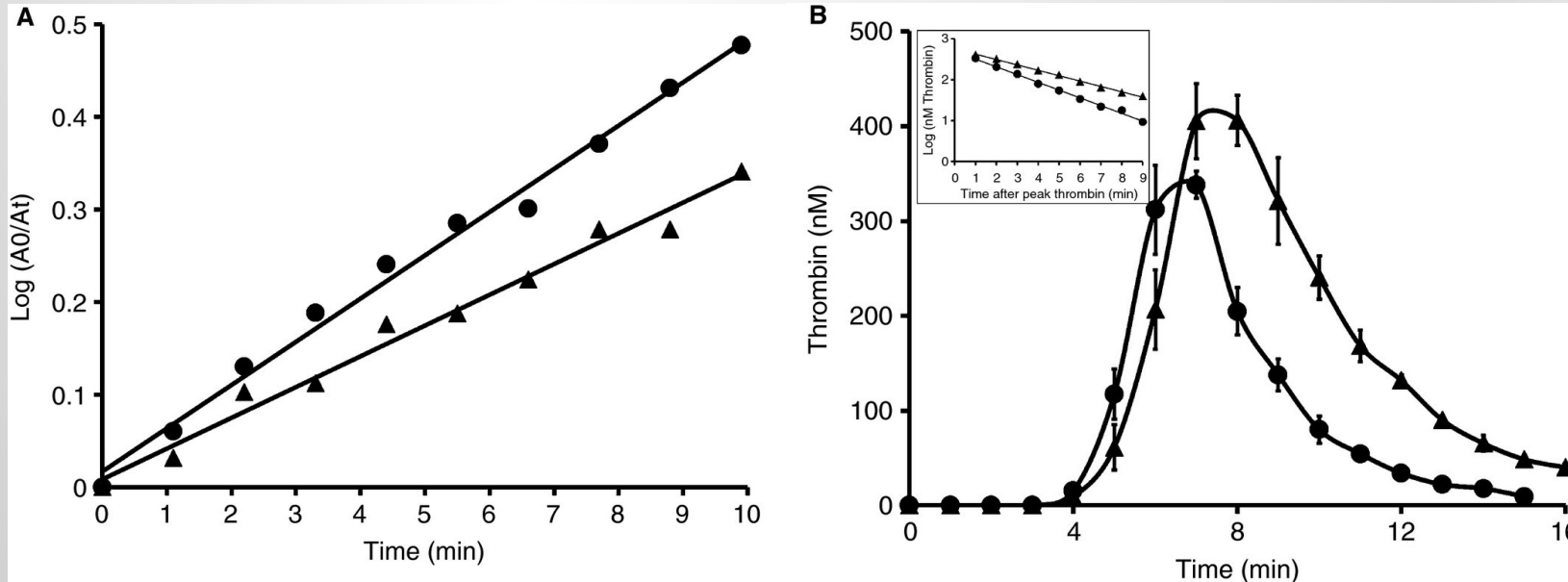
Klinische Relevanz?

1 Martini W et al. 2007. *Ann Surg*. Acidosis and coagulopathy: the differential effects on fibrinogen synthesis and breakdown in pigs. 246(5):831–835.

2 Engström M et al. 2006. *J Trauma*. Acidosis impairs the coagulation: a thromboelastographic study. 61(3):624–628.



Acidaemia and Coagulation



- A. Effect of pH on antithrombin efficacy
- B. Effect of pH on tissue factor-initiated thrombin generation in vitro

Reduction of factor complex assembly => reduced enzyme activity¹

- 50% at pH 7.2
- 20% at pH 6.8

Reduced inhibitor efficacy, but slightly enhanced clot formation dynamics
pH 7.0 (▲) vs. 7.4 (●) ex vivo²

Alleine wenig klinische Relevanz, wirkt synergistisch mit Hypothermie³

1 Murphy M et al. 2017. Practical Transfusion Medicine. 5th edn. Hoboken, NJ: John Wiley and Sons.

2 Gissel M et al. 2016. J Thromb Haemost. Effects of an acidic environment on coagulation dynamics. 14(10):2001-2010.

3 Dirkmann D et al. 2008. Anesth Analg. Hypothermia and acidosis synergistically impair coagulation in human whole blood. 106(6):1627-1632.

Meine Empfehlungen

1. Aggressives Wiedererwärmen $>34^{\circ}\text{C}$
2. Klinische Beurteilung der Koagulopathie
3. Azidose wirkt bei Hypothermie synergistisch

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Zusammenfassung

Trauma-induced coagulopathy

global inflammatory state after traumatic injury with

- coagulation derangements
- acidemia
- hypothermia

~25% of severely injured patients ¹

¹ Buzzard L et al. 2024. J Trauma Acute Care Surg. Trauma-induced coagulopathy: What you need to know. 96(2):179-185.

Lethal triad of death

1982 Trauma Research Center, University of Colorado, Denver

“bloody vicious cycle”: clinical and experimental data indicated that hypothermia & acidosis were conspicuous factors associated with early mortality in coagulopathic trauma patients ^{1,2}

Neue „Berlin-Definition“ Polytrauma ³

RR sys \leq 90 mmHg

GCS \leq 8

BE \leq -6.0

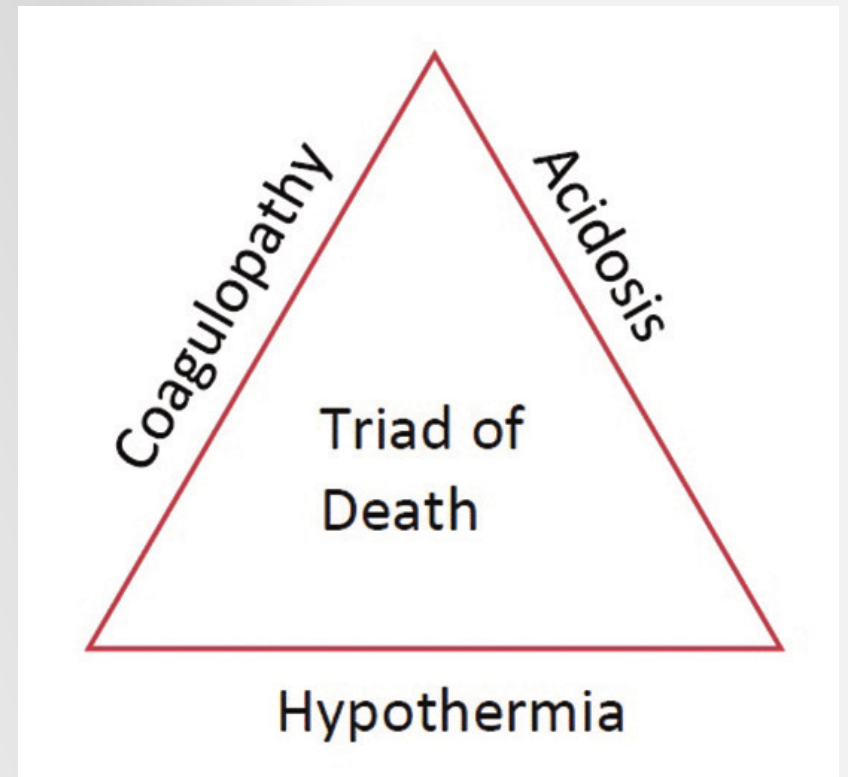
INR \geq 1.4/PTT \geq 40“

Age \geq 70

1 Kashuk J et al. 1982. J Trauma. Major abdominal vascular trauma--a unified approach. 22(8):672-679.

2 Dunn E et al. 1979. Surg Forum. Acidosis-induced coagulopathy. Surg Forum. 30:471-473

3 Pape H et al. 2014. J trauma Acute Care. The definition of polytrauma revisited: An international consensus process and proposal of the new 'Berlin definition'. 77(5):780-786.



Trauma-Related Hypocalcemia

$iCa^{2+} < 1.12$ mmol/L in 55% trauma patients on arrival ED (no blood before) ¹

$iCa^{2+} < 1.0$ mmol/L in 56% patients on arrival to ED ²

- ≥ 5 RBCs \uparrow (17.1% vs. 7.1%) | ≥ 10 RBCs \uparrow (8.2% vs. 2.2%)
- mortality \uparrow (15.5% vs. 8.7%)

F.IV: release of Ca^{2+} after PLT adhesion, binds to phospholipids after PLT activation, binding point for other coagulation factors ³

~3g citrate phosphate dextrose adenine/EK

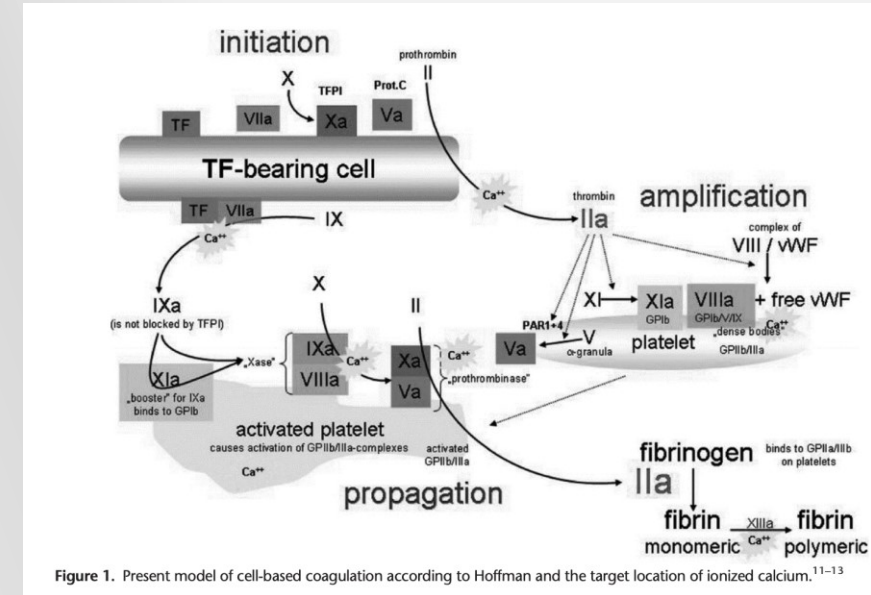


Figure 1. Present model of cell-based coagulation according to Hoffman and the target location of ionized calcium.¹¹⁻¹³

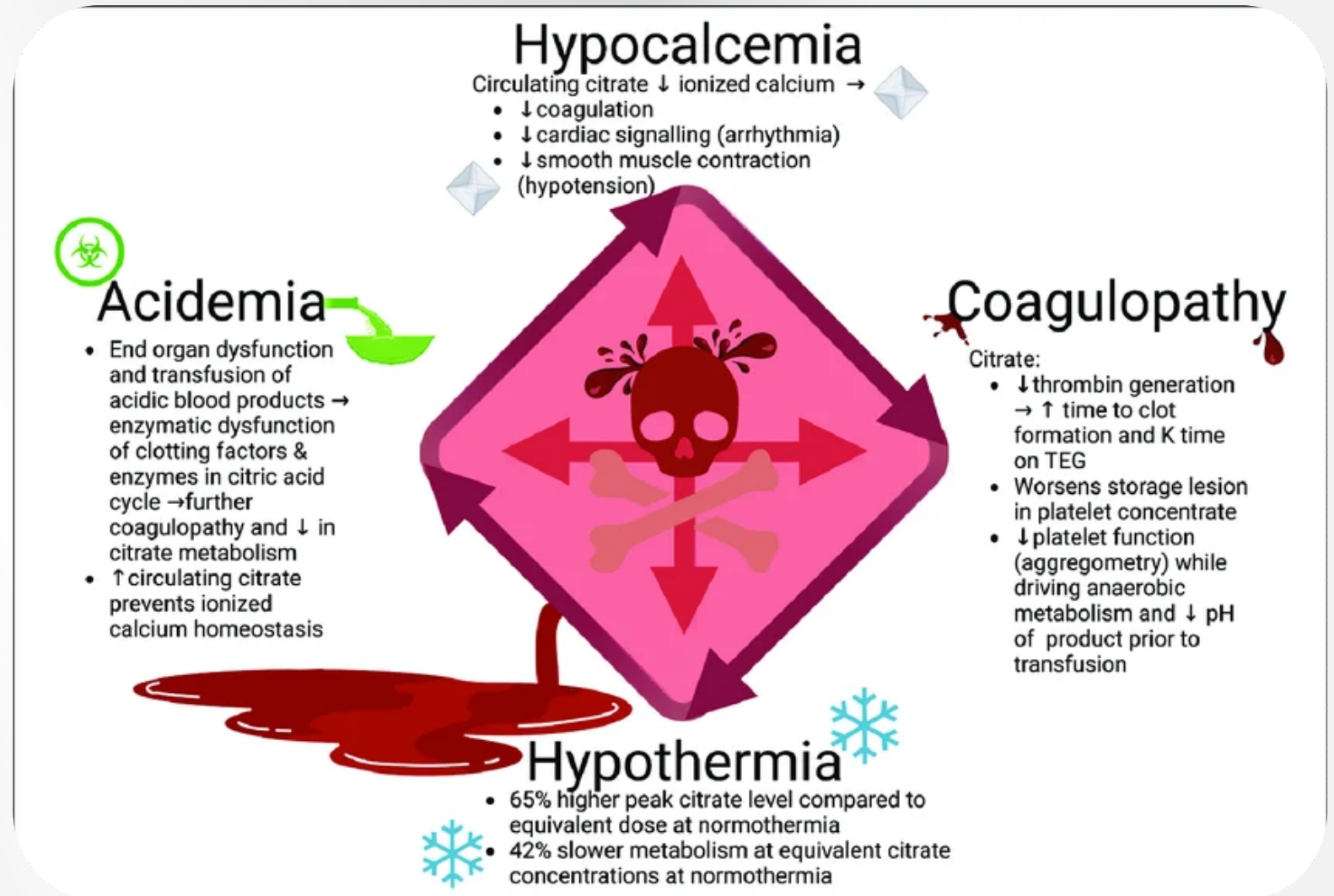
¹ Webster S et al. 2016. Emerg Med J. Ionised calcium levels in major trauma patients who received blood in the Emergency Department. 33(8):569-572

² Magnotti L et al. 2011. J Trauma. Admission ionized calcium levels predict the need for multiple transfusions: a prospective study of 591 critically ill trauma patients. 70(2):391-395

³ Hoffman M. 2003. Blood Rev. A cell-based model of coagulation and the role of factor VIIa. 17 Suppl 1:S1-5.

⁴ Amboss Auditor - Sekundäre Hämostase - Gerinnung an negativen Oberflächen - Vitamin K

Diamond of death



Schriner J et al. 2023. Crit Care Explor. Impact of Transfused Citrate on Pathophysiology in Massive Transfusion. 5(6):e0925.

Therapeutische Konsequenz

Critical gaps remain in translating hypocalcemia to practice

- Threshold values for defining hypocalcemia?
- Optimal timing of calcium administration?
- No evidence demonstrates calcium correction improving outcome!

Mein Vorgehen beim diamond of death

1. Ursache/Blutung therapieren
2. pH >7.2
3. iCa^{2+} >1.1 mmol/L
4. Früh Fibrinogen bis MCF Fibtem>9mm/Fibrinogen>150mg%
(50 – 70 – 100mg/kg)
5. Thrombozyten, PPSB, F.XIII

Dilutional coagulopathy

65% Blutverlust, Volumenersatz mit Gelatine, 250mg/kg Fibrinogen

Fries D et al. 2005. Br J Anaesth. Effect of fibrinogen on reversal of dilutional coagulopathy: a porcine model. 95(2):172-177.

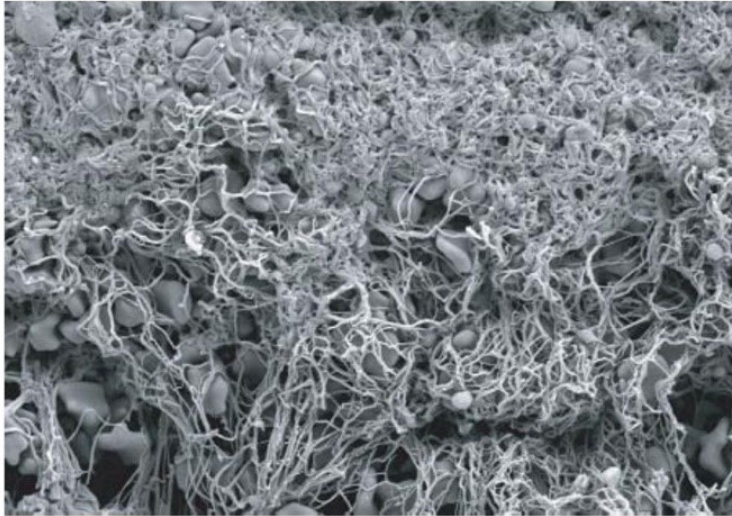


Fig 3 Electron microscopy scan of a 2000× magnified blood clot in non-diluted state: dense, branched, and meshed reticular fibrin network.

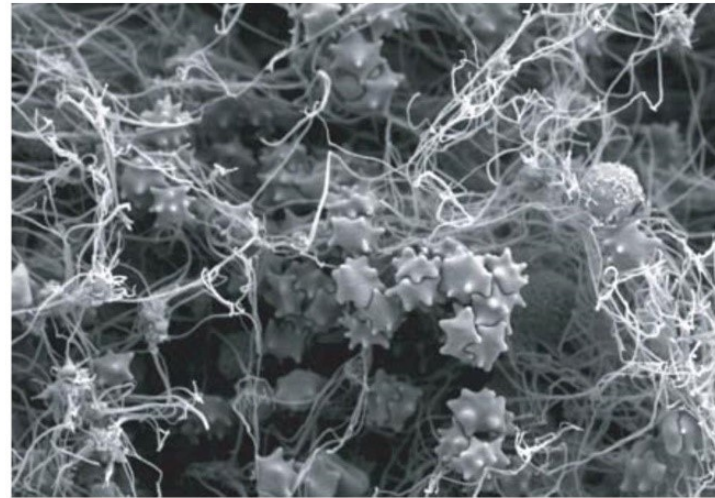


Fig 4 Electron microscopy scan of a 2000× magnified blood clot following approximately 65% haemodilution with gelatin: clearly rarified fibrin network.

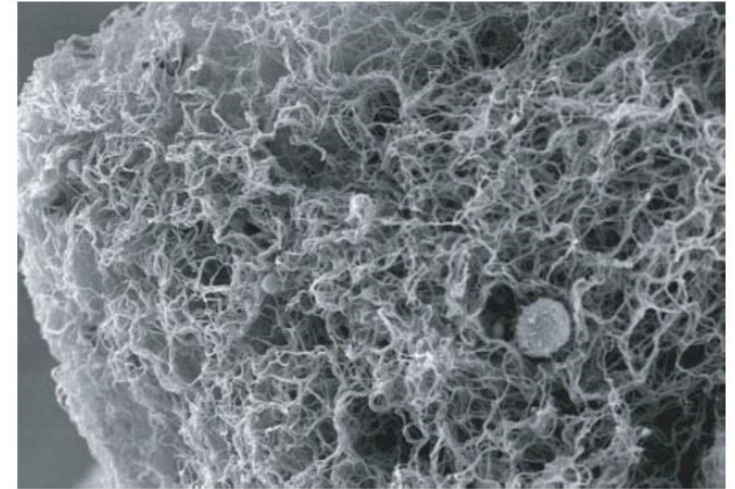


Fig 5 Electron microscopy scan of a 2000× magnified blood clot following administration of fibrinogen concentration to compensate for dilutional coagulopathy: in comparison with Figure 4 the fibrin network is again markedly compact. Because of the concomitant anaemia caused by 66% haemodilution, the clot shows only a few erythrocytes.

Volumentherapie

Lactic acidosis from traumatic tissue damage, hypoxia, and hemodilution exacerbated by resuscitation with crystalloids, which are acidotic solutions with high chloride content ¹

Trend towards more restrictive volumen resuscitation ²

- Crystalloids: cornerstone of initial resuscitation, less effective for severe volume depletion
- Colloids, gelatin-based solutions and albumin: used when crystalloids are inadequate
- Hydroxyethyl starch: no longer recommended

¹ Semler M et al. 2019. Am J Respir Crit Care Med. Balanced crystalloid solutions. 199(8):952–960.

² Markl-Le Levé A et al. 2025. Curr Opin Anaesthesiol. Fluid management in hemorrhagic shock. 38(3):316-322.

Restriktive Flüssigkeitssubstitution von Verlusten nach Rekap-Zeit, PPV etc.

- Gelofusin und Elomel

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Zusammenfassung

Sonderfall ECMO

va-ECMO: 32 Studien, n= 12.756

- KH-Mortalität 62.2%
- Blutung 48.5%
- Thrombose 13.4%
- ZNS-Komplikationen 12.5%

Rajsic et al. *Annals of Intensive Care* (2022) 12:93
<https://doi.org/10.1186/s13613-022-01067-9>


Annals of Intensive Care

RESEARCH

Open Access

Extracorporeal membrane oxygenation for cardiogenic shock: a meta-analysis of mortality and complications



Sasa Rajsic^{1†}, Benedikt Tremel^{1†}, Dragana Jadzic², Robert Breitkopf¹, Christoph Oberleitner¹, Marina Popovic Krneta³ and Zoran Bukumiric^{4*} 

Antikoagulation

Welche Dosis?

Welches Antikoagulans?

Welches Monitoring?

UFH , Argatroban, LMWH

Anticoagulation Monitoring during ECMO Support: Monitor or Flip a Coin?

The most appropriate tool for **anticoagulation monitoring** in patients receiving ECMO support is unclear

ECMO UFH ACT aPTT Anti Xa

Patients receiving **ECMO**
6 meta-analyses

Bleeding vs No Bleeding

- No significant difference in mean ACT
- Prolonged aPTT in patients with bleeding
- No significant difference in anti-Xa levels

Thrombosis vs No Thrombosis

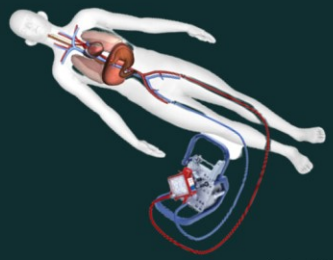
- No significant difference in mean ACT
- No difference in aPTT values
- Lower anti-Xa levels in patients with thrombosis

Positive moderate correlation between anti-Xa and UFH dose

Weak correlation between ACT and UFH infusion rates

i The increasing use of anti-factor Xa activity to monitor the effect of UFH appears appropriate. More sophisticated monitoring tools and careful clinical decision-making remain essential.

Rajsic et al. ECMO Anticoagulation: Monitor or Flip a Coin



Courtesy of Getinge AB

Rajsic S et al. 2024. Clin Cardiol. Anticoagulation Monitoring During ECMO Support: Monitor or Flip a Coin? 47(12):e70061.

- 1 Rajsic S et al. 2024. Anti-Xa-guided Anticoagulation With Unfractionated Heparin and Thrombosis During Extracorporeal Membrane Oxygenation Support: A Systematic Review and Meta-analysis. J Cardiothorac Vasc Anesth. 38(8):1662-1672.
- 2 Rajsic S et al. 2024. Anticoagulation Monitoring Using Activated Clotting Time in Patients Receiving Extracorporeal Membrane Oxygenation: A Meta-Analysis of Correlation Coefficients. J Cardiothorac Vasc Anesth. 38(11):2651-2660.
- 3 Schwaiger D et al. 2024. Association of Activated Clotting Time-Guided Anticoagulation with Complications during Extracorporeal Membrane Oxygenation Support: A Systematic Review and Meta-Analysis. J Cardiothorac Vasc Anesth. 38(12):3034-3042.
- 4 Rajsic S et al. 2024. Association of anti-factor Xa-guided anticoagulation with hemorrhage during ECMO support: A systematic review and meta-analysis. Clin Cardiol. 47(5):e24273.
- 5 Rajsic S et al. 2023. aPTT-guided anticoagulation monitoring during ECMO support: A systematic review and meta-analysis. J Crit Care. 77:154332.
- 6 Rajsic S et al. 2023. Association of aPTT-Guided Anticoagulation Monitoring with Thromboembolic Events in Patients Receiving V-A ECMO Support: A Systematic Review and Meta-Analysis. J Clin Med. 12(9):3224.

Antikoagulation bei ECMO

1. Antikoagulation an Patient:in anpassen
2. Bei UFH: antiXa (UFH) > CT Intem > aPTT > ACT
3. Bei Argatroban: Spiegel-Bestimmung

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Zusammenfassung

Koagulopathie bei Hypothermie, Azidose, Hämodilution, Trauma, ECMO

Temperatur $>34^{\circ}\text{C}$, pH >7.1 , $\text{Ca}^{2+} >1.0$

Klinische Beurteilung der Koagulopathie

Viskoelastisch gesteuerte Gerinnungstherapie

ECMO-Antikoagulation mit geeigneten Tests monitieren

Die Univ.-Klinik für Anästhesie und Intensivmedizin
und die Firma AOP Health laden ein zum

41. Innsbrucker UPDATE Anästhesie und Intensivmedizin

Zeit: **Mi, 27.5.2026** um **17.00 s.t.**

Ort: **gr. HS Chirurgie** (live - mit Videoaufzeichnung)

Vorträge können auf der Homepage www.ifimp.at nach der Veranstaltung nachgeschaut werden

AI meets NI – künstliche versus natürliche Intelligenz

Wann ist der Mensch besser – wann die Maschine? ... oder braucht es in Zukunft beides?

1. Priv.-Doz. Dr. Dr. med. Sebastian Schnaubelt: „Kurzwirksame Betablocker in der klinischen Praxis“ (Vortrag wird online eingespielt).
Leiter Department Prähospitale Forschung, Berufsrettung Wien
2. OA Dr. med. Armin Krösbacher: „Zwischen Alpen und Benchmark: Wie schneidet Tirol bei OHCA und IHCA ab?“
Ärztlicher Leiter Rettungsdienst Tirol
3. Prim. Prof. Dr. med. Dietmar Fries: „Antithrombin - unterschätztes Potential oder nebensächlicher Laborwert“
Leiter Anästhesie und operative Intensivmedizin, KH St. Vinzenz, Zams

Für die Organisation:



Ao.Univ.-Profⁱⁿ. Drⁱⁿ. Barbara Friesenecker



Priv.Doz. Dr. Benedikt Treml. MBA

Priv.Doz. Dr. Christopher Rugg, Priv. Dozⁱⁿ. Drⁱⁿ. Janett Kreuziger,

OA Dr. Benjamin Treichl, OÄ Drⁱⁿ. Petra Hillinger

Diese Fortbildungsveranstaltung ist im Rahmen des Diplomfortbildungsprogramms
der österreichischen Ärztekammer mit **3 Credit-Hours** anerkannt.

Univ.-Klinik für Anästhesie und Intensivmedizin, Anichstraße 35, A-6020 Innsbruck

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Daher werden weder die Organisation noch etwaige Kosten für Begleitpersonen von Firmen übernommen!

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