UNIVERSITÄTSKLINIKUM OWL
der Universität Bielefeld
Campus Bielefeld-Bethel

EVANGELISCHES KLINIKUM Bethel

Supportive Therapieansätze in der Neurointensivmedizin

Sebastian Rehberg

Universitätsklinik für Anästhesiologie, Intensiv-, Notfallmedizin, Transfusionsmedizin und Schmerztherapie
Universitätsklinikum OWL der Universität Bielefeld
Campus Bielefeld-Bethel

Bethel

Surgical Decompression for Space-Occupying Hemispheric Infarction

- **Systematischer Review und Metaanalyse**
- **7 RCTs mit 488 Patienten*innen**
- **Primärer Zielparameter: günstiges Outcome 1 Jahr nach Stroke**
- **günstiges Outcome = modified Rankin Scale (mRS) ≤ 3**

Reinink et al. JAMA Neurol 2021;78:208-16

Surgical Decompression for Space-Occupying Hemispheric Infarction

Table 3. Outcomes From the Pooled Data at 1 Year and 6 Months[a]

Outcome	No./total No. (%) of patients		RD	Crude OR (95% CI)	*P* value	Adjusted OR (95% CI	*P* value
	Surgery population	Medical population					
Primary outcome							
mRS score ≤3 at 1 y	87/234 (37)	37/254 (15)	(21)	3.23 (1.75-5.94)	<.001	2.95 (1.55-5.60)	.001
Secondary outcomes							
mRS score ≤2 at 1 y	39/234 (17)	12/254 (5)	(10)	2.91 (1.06-7.99)	.04	2.77 (0.97-7.88)	.06
mRS score ≤4 at 1 y	143/234 (61)	59/254 (23)	(38)	5.55 (3.42-9.00)	<.001	5.34 (3.26-8.74)	<.001
Death at 1 y	68/234 (29)	180/254 (71)	(-41)	0.16 (0.10-0.24)	<.001	0.16 (0.10-0.24)	<.001
mRS score ≤3 at 6 mo	60/202 (30)	19/222 (9)	(20)	4.85 (2.43-9.67)	<.001	4.67 (2.20-9.87)	<.001
mRS score ≤4 at 6 mo	118/202 (58)	43/222 (19)	(39)	6.07 (3.79-9.74)	<.001	5.67 (3.18-10.09)	<.001
Death at 6 mo	55/202 (27)	158/222 (71)	(44)	0.14 (0.09-0.22)	<.001	0.13 (0.08-0.22)	<.001
Shift analysis							
mRS score at 1 y	NA	NA	NA	5.29 (3.27-8.56)	<.001	4.95 (2.99-8.20)	<.001
mRS score at 6 mo	NA	NA	NA	6.38 (4.15-9.79)	<.001	6.62 (4.01-10.92)	<.001

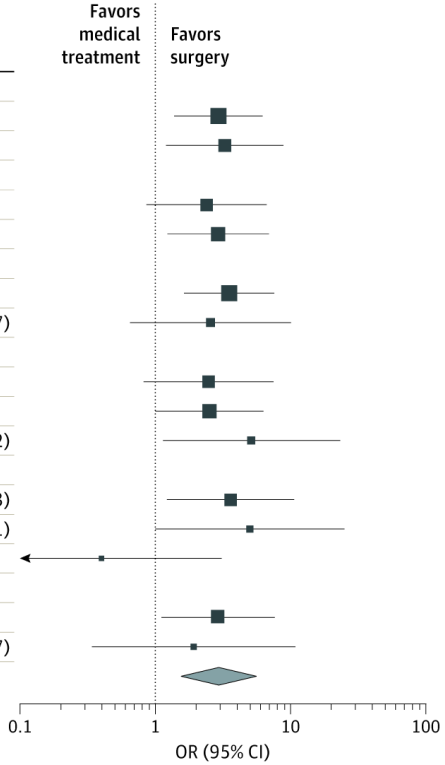
Abbreviations: mRS, modified Rankin Scale; NA, not applicable; RD, risk difference; OR, odds ratio.

[a] The RDs are pooled absolute RDs. The RDs and ORs are adjusted for age, sex, and presence of aphasia at randomization. All analyses are performed with a 1-stage model with random effects for trial baseline risk and treatment allocation.

Reinink et al. JAMA Neurol 2021;78:208-16

Surgical Decompression for Space-Occupying Hemispheric Infarction

Characteristic	No. (%) of patients: Surgery (n = 234)	Medical (n = 254)	OR (95% CI)
Aphasia (*P* = .43)			
Absent	44/128 (34)	21/138 (15)	2.93 (1.38-6.21)
Present	43/106 (41)	16/116 (14)	3.26 (1.20-8.85)
Sex (*P* = .34)			
Female	32/96 (33)	16/113 (14)	2.40 (0.86-6.66)
Male	55/138 (40)	21/141 (15)	2.91 (1.23-6.91)
Age, y (*P* = .48)			
≤ 60	54/118 (46)	23/117 (20)	3.52 (1.63-7.58)
>60	33/116 (28)	14/137 (10)	2.56 (0.65-10.07)
NIHSS score at baseline (*P* = .49)[a]			
≤ 20	23/55 (42)	11/42 (26)	2.48 (0.82-7.49)
21-25	29/72 (40)	16/83 (19)	2.51 (1.00-6.30)
>25	29/83 (35)	8/105 (8)	5.11 (1.14-22.82)
Time to randomization, h (*P* = .70)[b]			
< 24	19/68 (28)	8/71 (11)	3.60 (0.46-10.63)
24-48	19/78 (24)	8/87 (9)	5.00 (1.00-25.01)
>48	3/17 (18)	5/15 (33)	0.40 (0.05-3.09)
Vascular territory (*P* > .99)[c]			
MCA only	27/97 (28)	15/103 (15)	2.89 (1.11-7.56)
MCA and ACA and/or PCA	30/69 (44)	14/89 (16)	1.92 (0.34-10.87)
Summary			2.95 (1.55-5.60)



Reinink et al. JAMA Neurol 2021;78:208-16

! Take home messages !

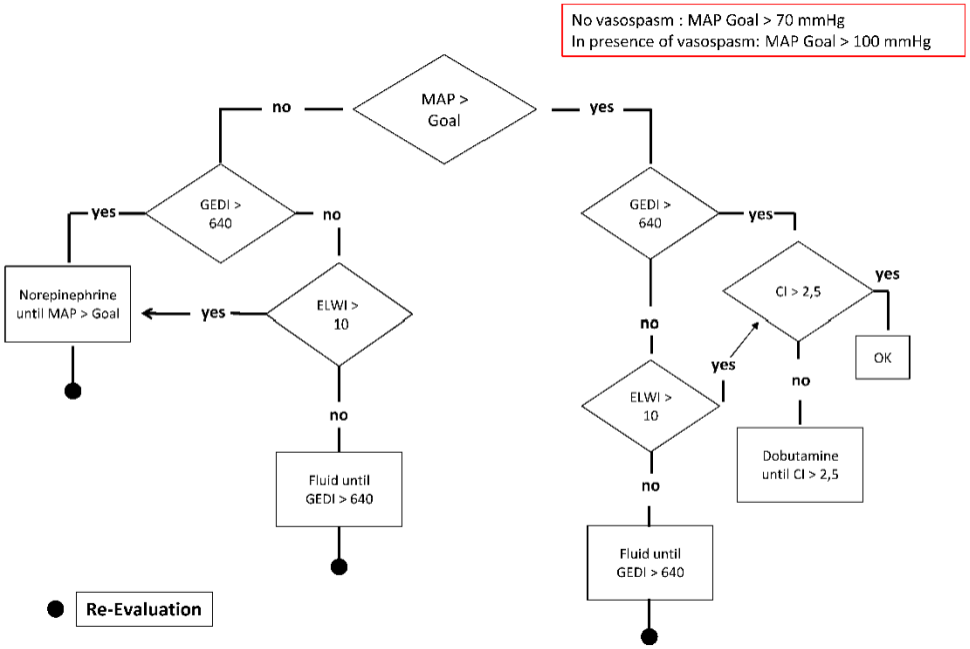
- **Bei raumfordernden halbseitigen Infarzierungen nach Schlaganfällen sollte eine chirurgische Dekompression erfolgen.**

Impact of Goal-Directed Therapy on Delayed Ischemia After Aneurysmal Subarachnoid Hemorrhage

- **randomisierte, kontrollierte Studie**
- **108 Patienten*innen mit aneurysmatischer SAB**
- **zielgerichtete hämodynamische vs. Standardtherapie**
- **primäre Zielparameter:**
  - **„delayed cerebral ischemia“**
  - **funktionelles Outcome 3 Monate nach Entlassung**

Anetsberger et al. Stroke 2020;51:2287-96

Impact of Goal-Directed Therapy on Delayed Ischemia After Aneurysmal Subarachnoid Hemorrhage



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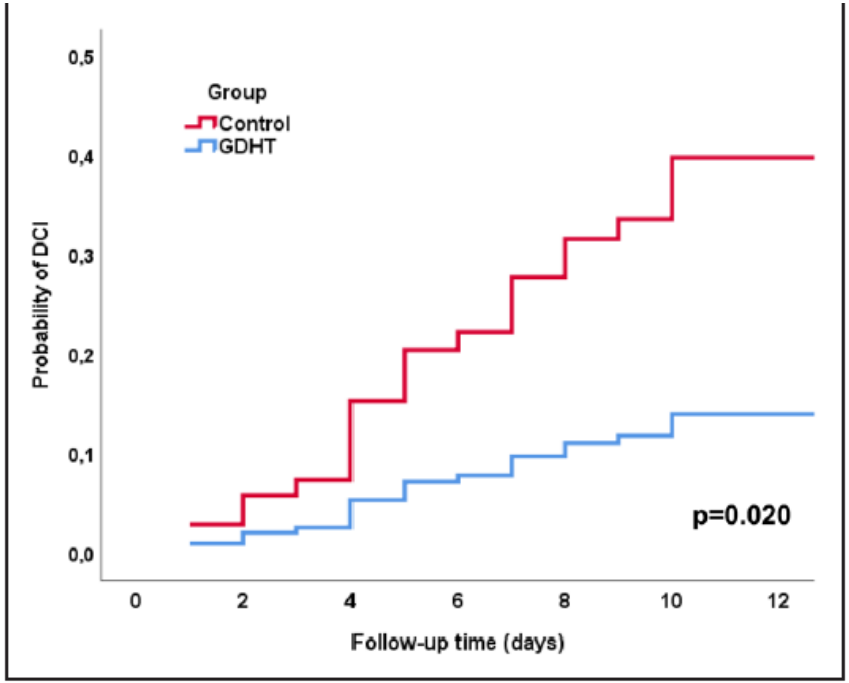
Impact of Goal-Directed Therapy on Delayed Ischemia After Aneurysmal Subarachnoid Hemorrhage



Anetsberger et al. Stroke 2020;51:2287-96

Impact of Goal-Directed Therapy on Delayed Ischemia After Aneurysmal Subarachnoid Hemorrhage

Outcome Events, n (%)	GDHT (n=54)	Control (n=54)	OR (95% CI)	*P* Value
Mortality at 3 mo	5 (9)	9 (17)	0.521 (0.16–1.67)	0.267
GOS (3 mo after discharge)	GDHT (n=53)	Control (n=54)	0.411 (0.19–0.9)	0.025
Minor or no deficits (GOS=5)	35 (66)	24 (44)		
Higher deficits to death (GOS≤4)	18 (34)	30 (56)		

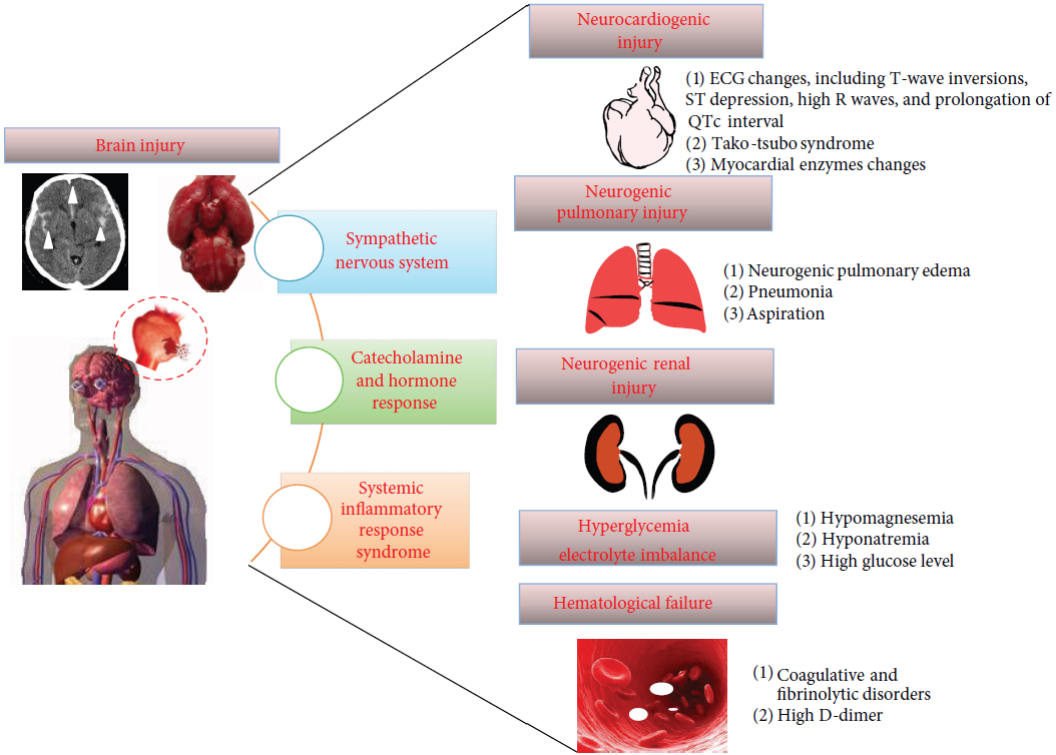
- **Noradrenalindosis: 0,27 ± 0,65 vs. 1,08 ± 1,81 µg/min**
- **Flüssigkeitsbilanz Tag 1-3 geringer**

Anetsberger et al. Stroke 2020;51:2287-96

! Take home messages !

Ein erweitertes kardiovaskuläres Monitoring mit assoziierten Therapiealgorithmen verbessert die hämodynamische Therapie der aSAB.

Subarachnoidalblutung: adrenerger Stress



Chen et al. BioMed Res Int 2014; 2014:858496

Persistierende Tachykardie nach SAB

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Prolonged Elevated Heart Rate is a Risk Factor for Adverse Cardiac Events and Poor Outcome after Subarachnoid Hemorrhage

- 447 Patienten*innen
- Persistierende Tachykardie:
  - >95 /min für >12h
  - Ausschlussdiagnose
- 39% der Patienten*innen

Schmidt et al. Neurocrit Care 2014;20:390-98

Persistierende Tachykardie nach SAB

UNIVERSITÄTSKLINIKUM OWL
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Characteristics	Prolonged elevated HR $N = 175$	Control group $N = 272$	OR (95 % CI)	P
Neurological				
Rebleed	18 (11 %)	19 (6 %)	2.1 (1.1–4.1)	0.03
Herniation	28 (18 %)	35 (11 %)	1.8 (1–3.1)	0.04
DCI from cerebral vasospasm	56 (32 %)	30 (11 %)	3.8 (2.3–6.2)	<0.001
Medical				
Fever > 101.5°F	92 (58 %)	113 (34 %)	2.6 (1.8–3.9)	<0.001
Pneumonia	53 (33 %)	55 (17 %)	2.5 (1.6–3.8)	<0.001
Sepsis	20 (12 %)	17 (5 %)	2.6 (1.3–5.2)	0.005
Cardiac				
Arrhythmias	33 (19 %)	38 (14 %)	1.4 (0.9, 2.4)	0.16
Cardiac arrest (in ICU)	3 (2 %)	7 (3 %)	0.7 (0.2, 2.6)	0.55
Myocardial infarction	29 (17 %)	14 (5 %)	3.7 (1.9, 7.2)	<0.001
Pulmonary edema	61 (35 %)	25 (9 %)	5.3 (3.2, 9.0)	<0.001
Hypertension	138 (79 %)	194 (71 %)	1.5 (0.96, 2.4)	0.08
Hypotension SBP < 90 mmHg	80 (46 %)	58 (21 %)	3.1 (2.0, 4.7)	<0.001

Schmidt et al. Neurocrit Care 2014;20:390-98

Betablockertherapie zur aSAB-Therapie

Beta-Blockade in Aneurysmal Subarachnoid Hemorrhage: a Systematic Review and Meta-Analysis

- **vorbestehende Medikation und neu angesetzte Therapie**
- **geringe Qualität und hohe Heterogenität der Studien**
- **Therapie:**
  - **50 % nicht-selektive Betablocker (Propanolol)**
  - **50% ß$_1$-selektive Betablocker (Landiolol, Metoprolol)**

Ramesch et al. Neurocrit Care 2020; 33:508-515

Betablockertherapie zur aSAB-Therapie

Beta-Blockade in Aneurysmal Subarachnoid Hemorrhage: a Systematic Review and Meta-Analysis

Study or Subgroup	Beta-blockade Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Crago 2014	0	19	21	211	2.1%	0.25 [0.02, 3.92]
Duello 2013	6	18	40	116	32.1%	0.97 [0.48, 1.95]
Hamann 1993	2	11	9	14	9.1%	0.28 [0.08, 1.05]
Kawaguchi 2010	3	28	1	28	3.2%	3.00 [0.33, 27.12]
Liang 2013	2	21	17	109	8.2%	0.61 [0.15, 2.45]
Neil-Dwyer 1985	13	111	21	93	39.1%	0.52 [0.28, 0.98]
Wang 1991	2	50	5	55	6.2%	0.44 [0.09, 2.17]
Total (95% CI)		**258**		**626**	**100.0%**	**0.63 [0.42, 0.93]**
Total events	28		114			

Heterogeneity: Tau² = 0.00; Chi² = 5.85, df = 6 (P = 0.44); I² = 0%
Test for overall effect: Z = 2.31 (P = 0.02)

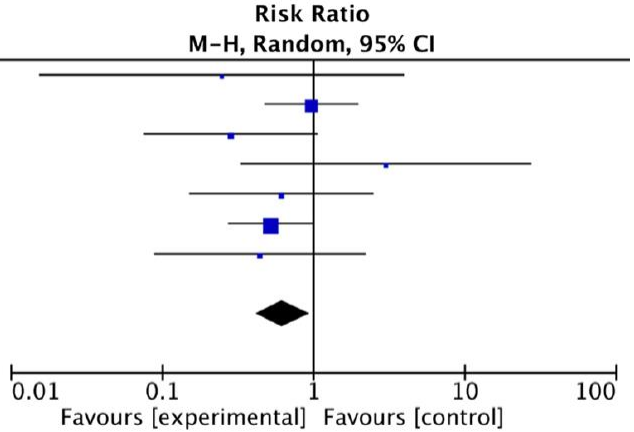


Fig. 2 Forest plot of studies (observational and RCT) comparing the effect of beta-blocker therapy with control on mortality

Ramesch et al. Neurocrit Care 2020; 33:508-515

Keine Standardtherapie !

Beta-Blockers for Subarachnoid Hemorrhage: When Should We Use Them?

- **Aktuell keine Empfehlung !**
- **Hämodynamische Stabilität ist Voraussetzung.**
- **CAVE: Blutdruckabfall**
- **zielorientiert (HF als Marker für adrenergen Stress?)**
- **„…the use of beta-blockers after aSAH has specific indications and moments, so a generalized recommendation might not be in place."**

Nino et al. Neurocrit Care 2020; 33:851-52

Betablockertherapie nach Schädelhirntrauma

Beta-Blocker Therapy in Severe Traumatic Brain Injury: A Prospective Randomized Controlled Trial

- 219 Patienten*innen mit schwerem SHT
- 24h nach Trauma, hämodynamisch stabil
- Intervention: 20 mg Propanolol p.o. vs. Plazebo alle 12 h für 10 d
- primäre Zielparameter:
  - Krankenhaussterblichkeit
  - funktionelles Outcome bei Entlassung und nach 6 Monaten nach (GOSE)

Khalili et al. World J Surg 2020; 44:1844-53

Betablockertherapie nach Schädelhirntrauma

Beta-Blocker Therapy in Severe Traumatic Brain Injury: A Prospective Randomized Controlled Trial

Gesamte Studienpopulation

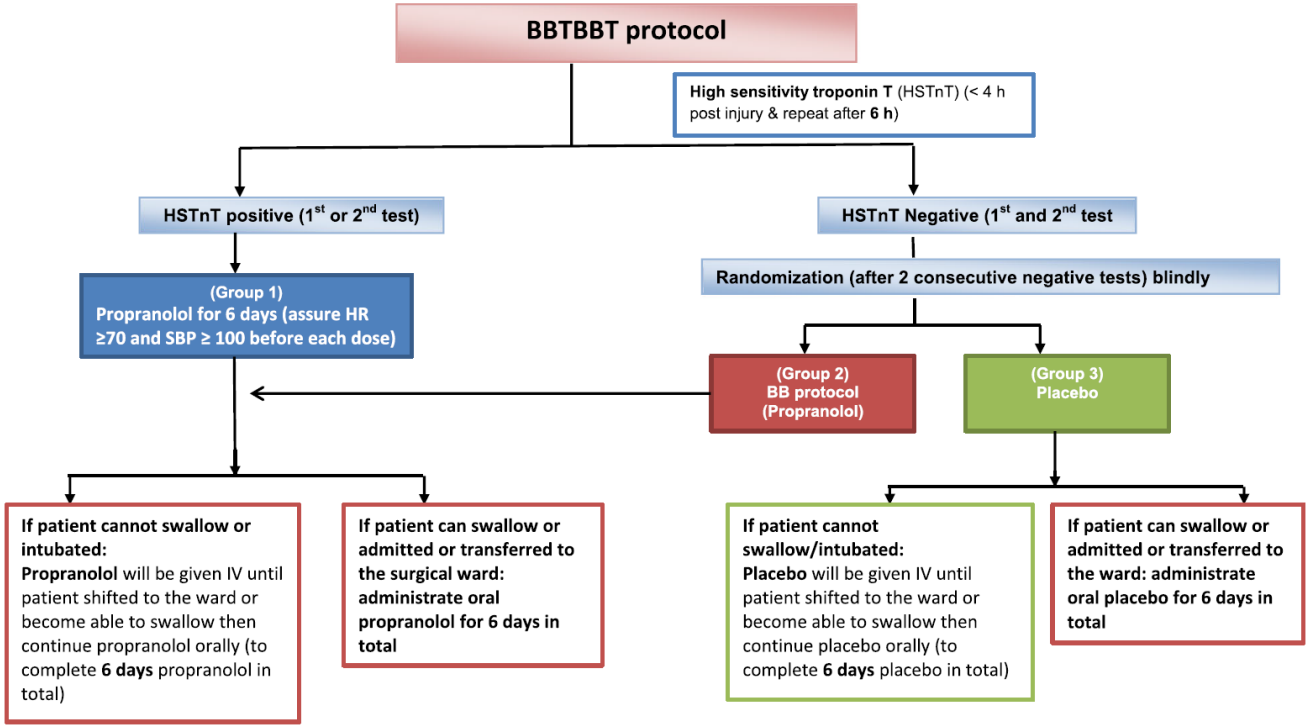
	Total $n = 219$	BB (−) $n = 120$	BB (+) $n = 99$	p
Mortality	28 (12.8)	20 (16.7)	8 (8.1)	0.058
GOS-E at discharge ≥5	149 (69.3)	78 (66.7)	71 (72.4)	0.36
GOS-E at 6 months ≥5	176 (81.5)	93 (77.5)	83 (86.5)	0.09

Isoliertes SHT

	Total $n = 154$	BB (−) $n = 86$	BB (+) $n = 68$	p
Mortality	19 (12.3)	16 (18.6)	3 (4.4)	0.012
GOS-E at discharge ≥5	109 (70.8)	56 (65.1)	53 (77.9)	0.08
GOS-E at 6 months ≥5	128 (84.8)	68 (79.1)	60 (92.3)	0.04

Khalili et al. World J Surg 2020; 44:1844-53

Beta blocker use in traumatic brain injury based on the high-sensitive troponin status (BBTBBT): methodology and protocol implementation of a double-blind randomized controlled clinical trial



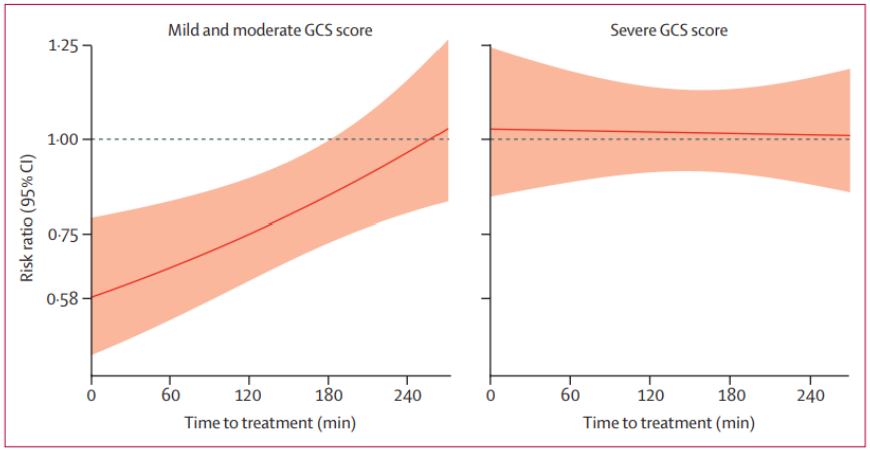
El-Menyar et al. Trials 2021;22:890

! Take home messages !

- **Persistierender adrenerger Stress verschlechtert das Outcome sowohl nach aSAB als auch nach TBI.**
- **Betablocker stellen eine potenziell wirksame Therapieoption dar.**
- **Die aktuelle Datenlage ist für eine Therapieempfehlung jedoch nicht ausreichend.**

Tranexamsäure und TBI

Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH-3): a randomised, placebo-controlled trial



Interpretation Our results show that tranexamic acid is safe in patients with TBI and that treatment within 3 h of injury reduces head injury-related death. Patients should be treated as soon as possible after injury.

Roberts et al. Lancet 2019;394:1713-23

Tranexamsäure und TBI

Efficacy and safety of tranexamic acid in acute traumatic brain injury: a systematic review and meta-analysis of randomized-controlled trials

- **9 randomisierte, kontrollierte Studien**
- **14.747 Patienten*innen mit TBI**

Take-home message

In patients with acute TBI, TXA probably has no effect on mortality or disability. The use of TXA probably does not increase the risk of adverse events.

Lawati et al. Intensive Care Med 2021;47:14-27

Tranexamsäure und TBI

JAMA Neurology | Original Investigation

Association Between Prehospital Tranexamic Acid Administration and Outcomes of Severe Traumatic Brain Injury

Sebastiaan M. Bossers, MD; Stephan A. Loer, PhD; Frank W. Bloemers, PhD; Dennis Den Hartog, PhD; Esther M. M. Van Lieshout, PhD; Nico Hoogerwerf, PhD; Joukje van der Naalt, PhD; Anthony R. Absalom, MD; Saskia M. Peerdeman, PhD; Lothar A. Schwarte, PhD; Christa Boer, PhD; Patrick Schober, PhD; for the BRAIN-PROTECT collaborators

- **Multizentrische Observationsstudie**
- **1.827 Patienten*innen mit Verdacht auf TBI**
- **Intervention: prähospitale Gabe von Tranexamsäure**

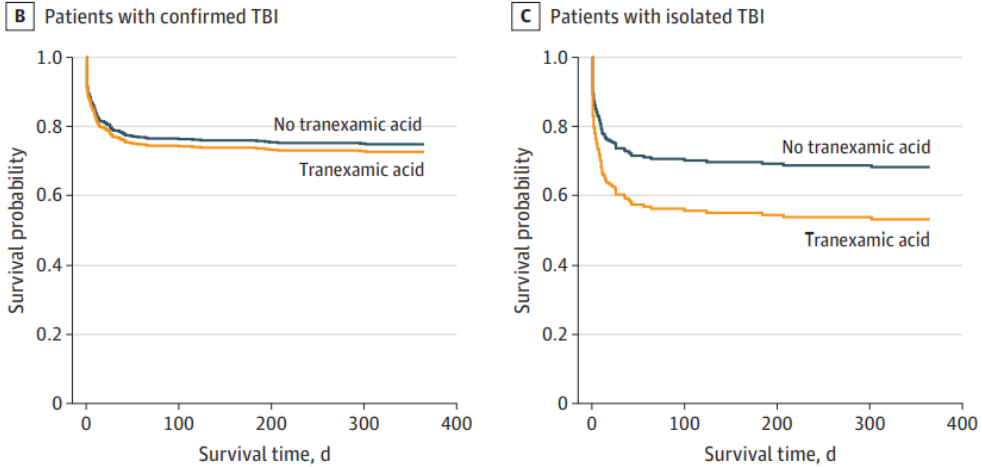
Bossers et al. JAMA Neurol 2021;78:338-45

Tranexamsäure und TBI

JAMA Neurology | Original Investigation

Association Between Prehospital Tranexamic Acid Administration and Outcomes of Severe Traumatic Brain Injury

Sebastiaan M. Bossers, MD; Stephan A. Loer, PhD; Frank W. Bloemers, PhD; Dennis Den Hartog, PhD; Esther M. M. Van Lieshout, PhD; Nico Hoogerwerf, PhD; Joukje van der Naalt, PhD; Anthony R. Absalom, MD; Saskia M. Peerdeman, PhD; Lothar A. Schwarte, PhD; Christa Boer, PhD; Patrick Schober, PhD; for the BRAIN-PROTECT collaborators



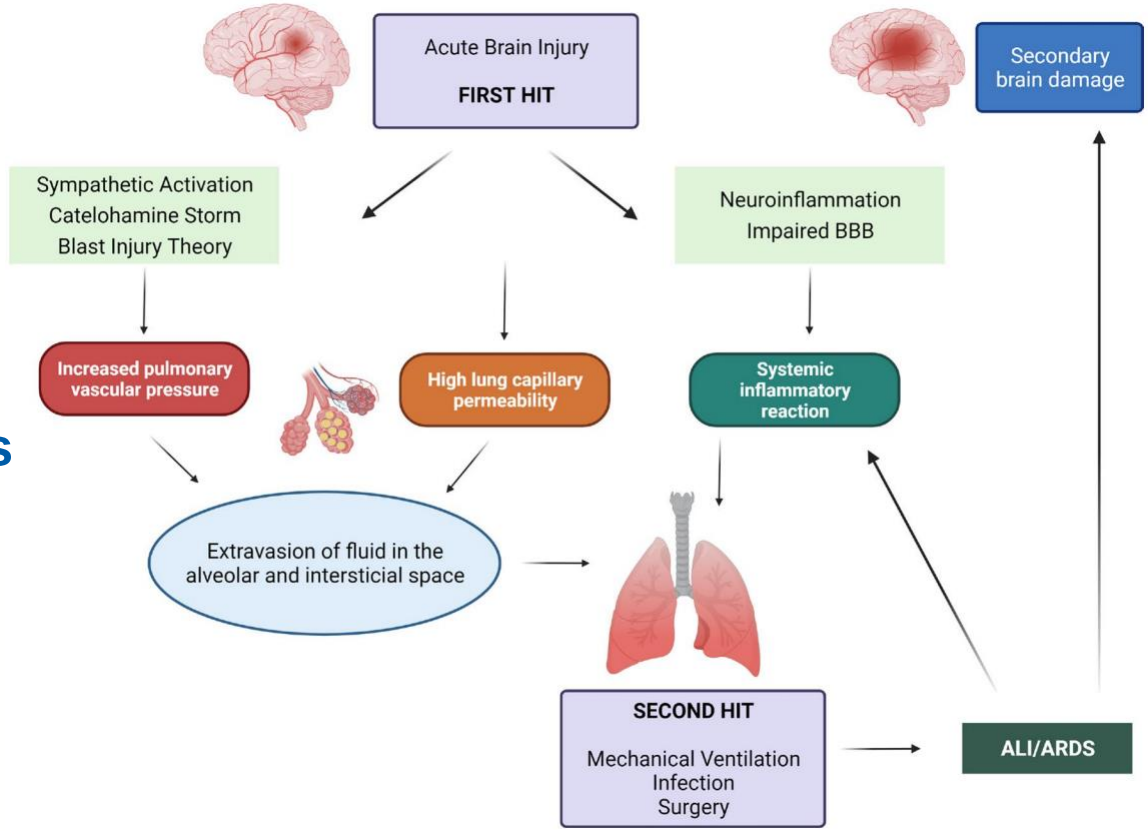
Conclusions

To our knowledge, this cohort study is the first to demonstrate an association between tranexamic acid and increased mortality in patients with isolated severe TBI. This finding suggests that administration of tranexamic acid should be avoided in such patients.

Bossers et al. JAMA Neurol 2021;78:338-45

Brain-Lung interaction in acute brain injury

- **Pneumonie**
  - **Aspiration**
  - **Beatmungsassoziiert**
- **Neurogenes Pulmonales Ödem**



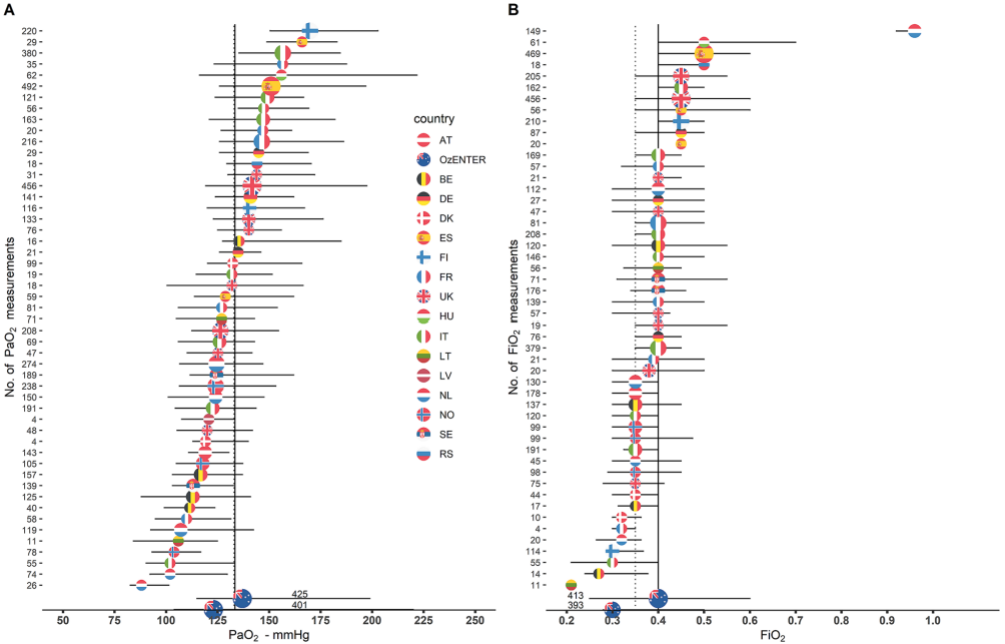
Ziaka et al. Crit Care 2021;25:358

High arterial oxygen levels and supplemental oxygen administration in traumatic brain injury: insights from CENTER-TBI and OzENTER-TBI

- **Sekundäranalyse von 2 multizentrischen Observationsstudien aus Europa und Australien**
- **>1200 Patienten*innen mit TBI**
- **täglich höchste FiO_2- und PaO_2-Werte in der ersten 7 Tagen**

Rezoagli et al. Intensive Care Med 2022;48:1709-25

High arterial oxygen levels and supplemental oxygen administration in traumatic brain injury: insights from CENTER-TBI and OzENTER-TBI



Rezoagli et al. Intensive Care Med 2022;48:1709-25

High arterial oxygen levels and supplemental oxygen administration in traumatic brain injury: insights from CENTER-TBI and OzENTER-TBI

CENTER-TBI	6-month GOSE N = 912 patients, 489 GOSE ≤ 4			6-month mortality N = 912 patients, 225 died		
Model 1	**OR[a]**	**95% CI**	***p* value**	**OR[a]**	**95% CI**	***p* value**
PaO_{2max} (for 10 mmHg increase)	1.02	1–1.04	0.014	1.03	1.01–1.05	0.002
PaO_{2mean} (for 10 mmHg increase)	1.03	1–1.07	0.059	1.08	1.04–1.13	< 0.001
ΔPaO_{2mean} (for 10 mmHg increase)[b]	1.07	1.03–1.12	0.001	1.14	1.08–1.20	< 0.001
	6-month GOSE N = 764 patients, 407 GOSE ≤ 4			6-month mortality N = 764 patients, 175 died		
Model 2	**OR[a]**	**95% CI**	***p* value**	**OR[a]**	**95% CI**	***p* value**
Logarithm GFAP	1.51	1.33–1.71	< 0.001	1.51	1.29–1.77	< 0.001
PaO_{2max} (for 10 mmHg increase)	1.02	1–1.03	0.064	1.03	1.01–1.05	0.008
Logarithm GFAP	1.52	1.34–1.72	< 0.001	1.52	1.3–1.78	< 0.001
PaO_{2mean} (for 10 mmHg increase)	1.03	0.99–1.07	0.092	1.09	1.04–1.14	0.001
Logarithm GFAP	1.52	1.34–1.72	< 0.001	1.53	1.3–1.81	< 0.001
ΔPaO_{2mean} (for 10 mmHg increase)	1.05	1–1.11	0.031	1.14	1.08–1.21	< 0.001
	6-month GOSE N = 877 patients, 470 GOSE ≤ 4			6-month mortality N = 877 patients, 212 died		
Model 3	**OR[c]**	**95% CI**	***p* value**	**OR[c]**	**95% CI**	***p* value**
FiO_{2max} (for 0.1 increase)	1.03	0.96–1.1	0.453	1.18	1.08–1.29	< 0.001
FiO_{2mean} (for 0.1 increase)	1.02	0.92–1.14	0.694	1.31	1.13–1.51	< 0.001
ΔFiO_{2mean} (for 0.1 increase)	1.03	0.84–1.27	0.761	1.46	1.13–1.88	0.004

Rezoagli et al. Intensive Care Med 2022;48:1709-25

! Take home messages !

Unabhängig vom Schweregrad der traumatischen Hirnschädigung sind hohe FiO_2- sowie hohe PaO_2-Werte in den ersten 7 Tagen mit einer erhöhten Sterblichkeit innerhalb von 6 Monaten assoziiert.

Mechanical ventilation in patients with acute brain injury: recommendations of the European Society of Intensive Care Medicine consensus

- **Indikationen zur Intubation**
- **Nicht-invasive Beatmungsverfahren**
- **Spezifischer Beatmungseinstellungen und Zielparameter**
- **Spezifischer Zielwerte für pH, PaO_2 und $PaCO_2$**
- **Sicherheit und Effekte : Relaxierung, Bauchlage und ECMO**
- **Weaning und Extubation**
- **Tracheostomy**

Robba et al. Intensive Care Med 2020;46:2397-410

Management of moderate to severe traumatic brain injury: an update for the intensivist

Parameter	Key messages	Clinical recommendation
PaO_2	Hypoxia is a well-known cause of secondary brain damage Hyperoxia seems to worsen outcome by increasing cerebral inflammation and reactive oxygen species	Target PaO_2 = 80–120 mmHg
$PaCO_2$	Hypercapnia may cause cerebral vasodilation and increased ICP Hypocapnia may reduce ICP but can cause cerebral vaso-constriction and ischemia	Target $PaCO_2$ = 35–45 mmHg In case of intracranial hypertension: $PaCO_2$ = 35–38 mmHg as Tier 1 $PaCO_2$ = 32–35 mmHg as Tier 2, preferably with additional $PbtO_2$-monitoring $PaCO_2$ = 30–32 mmHg (briefly) as rescue for refractory intracranial hypertension (not routinely recommended)
TV/Pplat	High TV and Pplat increase the risk of ventilator-induced lung injury in brain injured patients Low TV may cause hypercapnia and increased ICP	TV = 6–8 mL/kg PBW, driving pressure < 15 cmH_20, Pplat 18–25 cmH_20
PEEP	PEEP can improve oxygenation and prevent atelectasis PEEP can lead to increased intrathoracic pressure, reduced jugular venous outflow, and hemodynamic instability Alveolar hyperdistention caused by excessive levels of PEEP can increase $PaCO_2$ values	PEEP should be set according to the principles applied in the general ICU population, considering systemic oxygenation, respiratory mechanics (compliance), and hemodynamic status
Recruitment manoevers	RM may improve oxygenation RM can cause hemodynamic instability and reduction of CPP RM can increase intrathoracic pressure and reduce jugular venous outflow	RM only as rescue therapy (hypoxemia responsive to PEEP, and considering/preventing the risk of hemodynamic instability)

Meyfroidt et al. Intensive Care Med 2022;48:649-55

Management of moderate to severe traumatic brain injury: an update for the intensivist

Prone positioning	May improve oxygenation and improve outcomes in hypoxemic respiratory failure May improve cerebral oxygenation Risk of hemodynamic instability Risk of ICP catheter dislocation	May be taken in consideration as rescue therapy, considering risks and benefits to improve systemic and cerebral oxygenation
iNO	May improve systemic and cerebral oxygenation No definite evidence regarding outcome benefit	Should be considered in case of refractory hypoxemia with pulmonary hypertension
$ECCO_2R$	Can allow protective ventilation with $PaCO_2$ control Quick reduction of $PaCO_2$ could lead to cerebral vasoconstriction	Can be considered in TBI without active intracranial bleeding None or reduced dose of heparin for cannulation should be applied
ECMO	Can improve oxygenation and control $PaCO_2$, but often requires systemic anticoagulation and thus increases the risk of bleeding Quick changes in $PaCO_2$ and PaO_2 can lead to cerebral vasoconstriction, loss of autoregulation and intracerebral complications	Can be considered in TBI without active intracranial bleeding None or reduced dose of heparin for cannulation should be applied

Meyfroidt et al. Intensive Care Med 2022;48:649-55

Empfehlungen

Management of moderate to severe traumatic brain injury: an update for the intensivist

- **Ziel-CPP: 60 – 70 mmHg**
- **Noradrenalin als Vasopressor der 1. Wahl**
- **engmaschiges Monitoring des Volumenstatus**
- **engmaschiges Monitoring der kardiovaskulären Funktion**

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Vielen Dank für die Aufmerksamkeit

Besinnliche Weihnachtsfeiertage
und
einen Guten Rutsch ins neue Jahr !