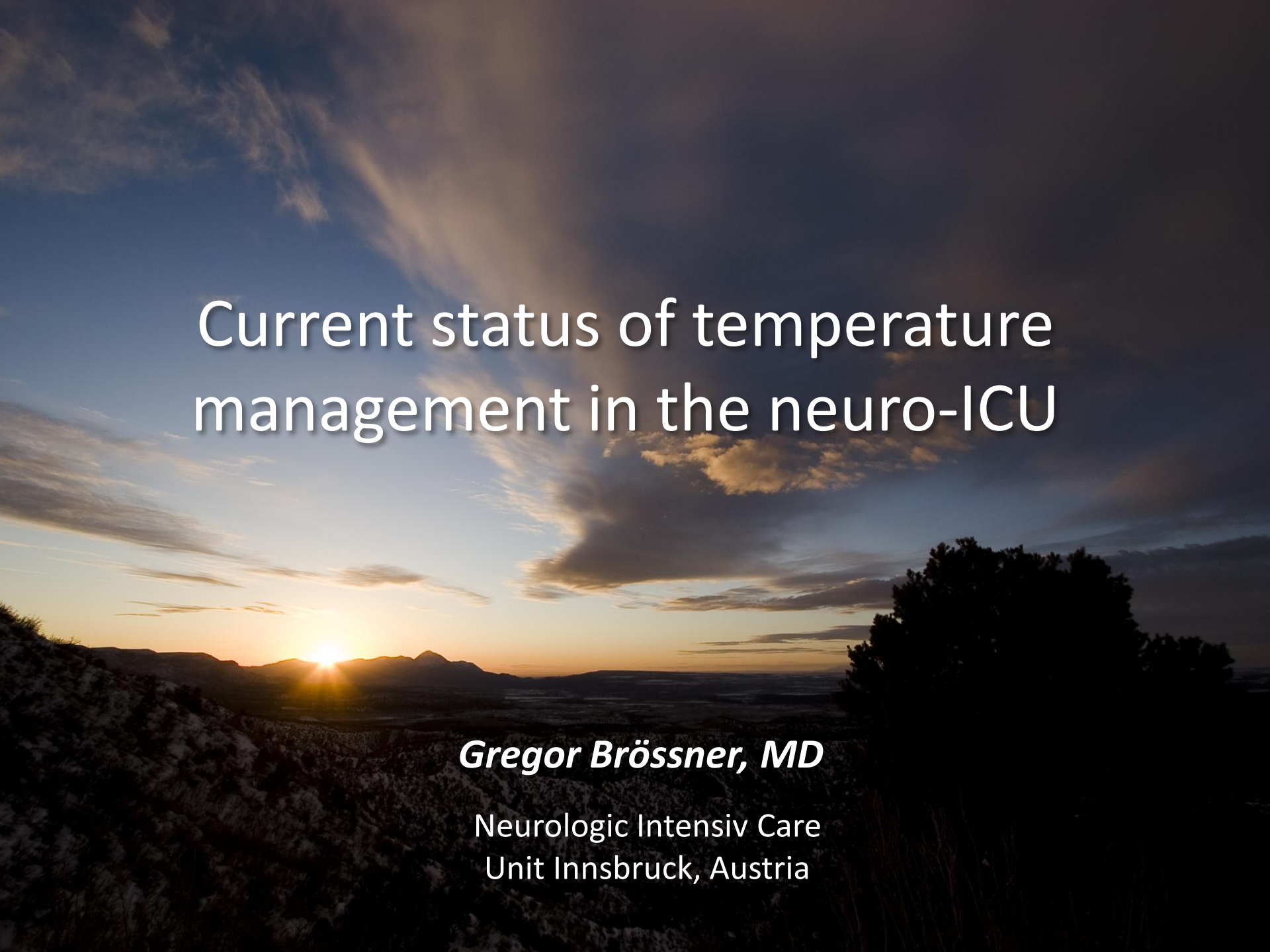


Current status of temperature management in the neuro-ICU

Gregor Brössner, MD

Neurologic Intensiv Care
Unit Innsbruck, Austria

Disclosures:

Gregor Brössner has recieved an unrestricted Grant by Alsius Corp®.. Speakers honoraria and travel grants from Zoll® Corp. and Euromed.

Outline:

Pathophysiological effects of fever
Mechanisms of therapeutic hypothermia
Practical aspects of hypothermia
Concept of prophylactic normothermia

Ongoing trials / future indications of temperature management

Discussion

40 minutes

Negative effects of fever, „secondary neuronal injury“ I:

Impact of Fever on Outcome in Patients With Stroke and Neurologic Injury: A Comprehensive Meta-Analysis

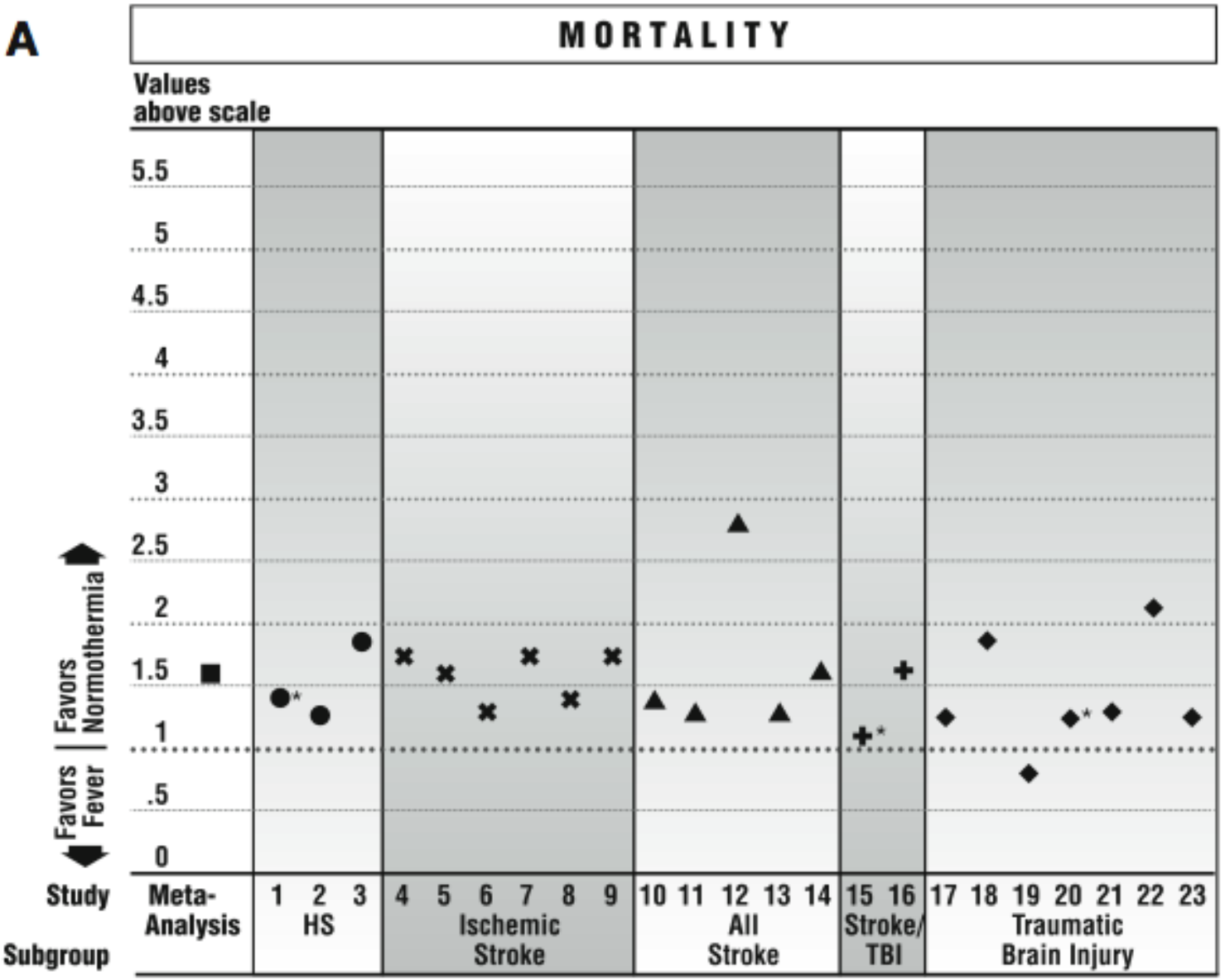
David M. Greer, Susan E. Funk, Nancy L. Reaven, Myrsini Ouzounelli and Gwen C. Uman

Stroke

Metaanalysis of 39 studies and 14.000 patients

Outcome Measure	No. of Articles/ Hypotheses*	RR	Fever/Higher Body Temperature Associated Significantly With
Mortality	24/24	1.5	Death
GOS	9/11	1.3	Neurological deficit/death
BI	8/10	1.9	More dependence
mRS	5/5	2.2	Lower functioning
CSS	5/8	1.4	Greater severity
ICU LOS	6/6	2.8	Longer ICU stay
Hospital LOS	3/3	3.2	Longer hospital stay

Negative effects of fever, „secondary neuronal injury“ II:



Mechanisms of temperaturemanagement:

Primary Injury:
Traumatic brain injury (TBI)
Stroke
Hypoxia
intracerebral hematoma
metabolic

ICP= intracranial pressure

Mechanisms of temperaturemanagement:

Primary Injury:
Traumatic brain injury (TBI)
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Hypoxia
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metabolic

Secondary Injury:
Brain edema
Stroke (vasospasm)
elektrolyte disturbance(Ca, Na/K)
neuro-excitation (seizures)

ICP= intracranial pressure

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Primary Injury:
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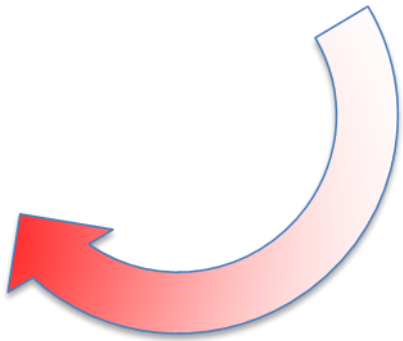
elevation of ICP



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Mechanisms of temperaturemanagement:

Primary Injury:
Traumatic brain injury (TBI)
Stroke
Hypoxia
intracerebral hematoma
metabolic

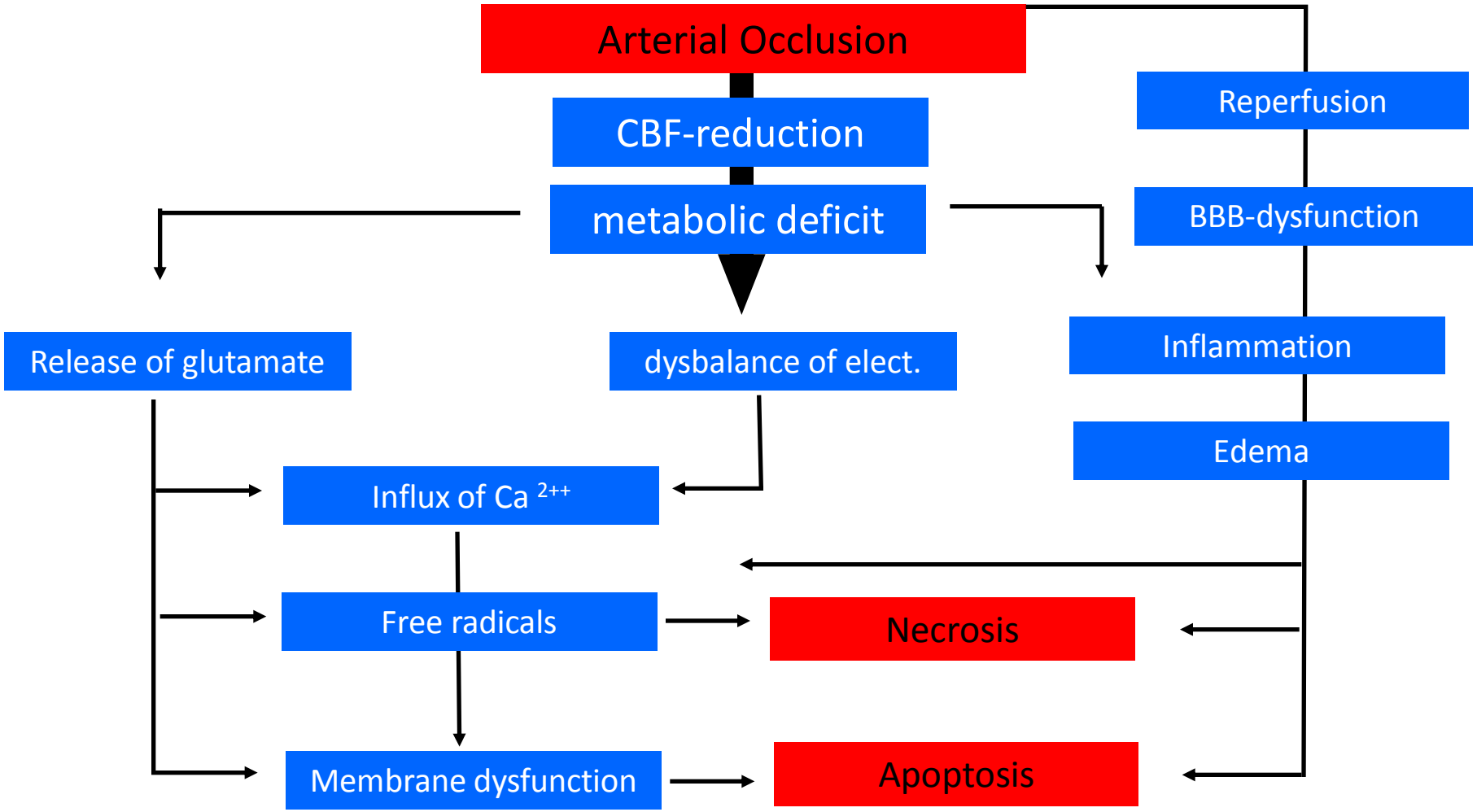
Secondary Injury:
Brain edema
Stroke (vasospasm)
elevated ICP
disturbance (Ca, Na/K)
neuro-excitation (seizures)

Normo-/Hypothermia

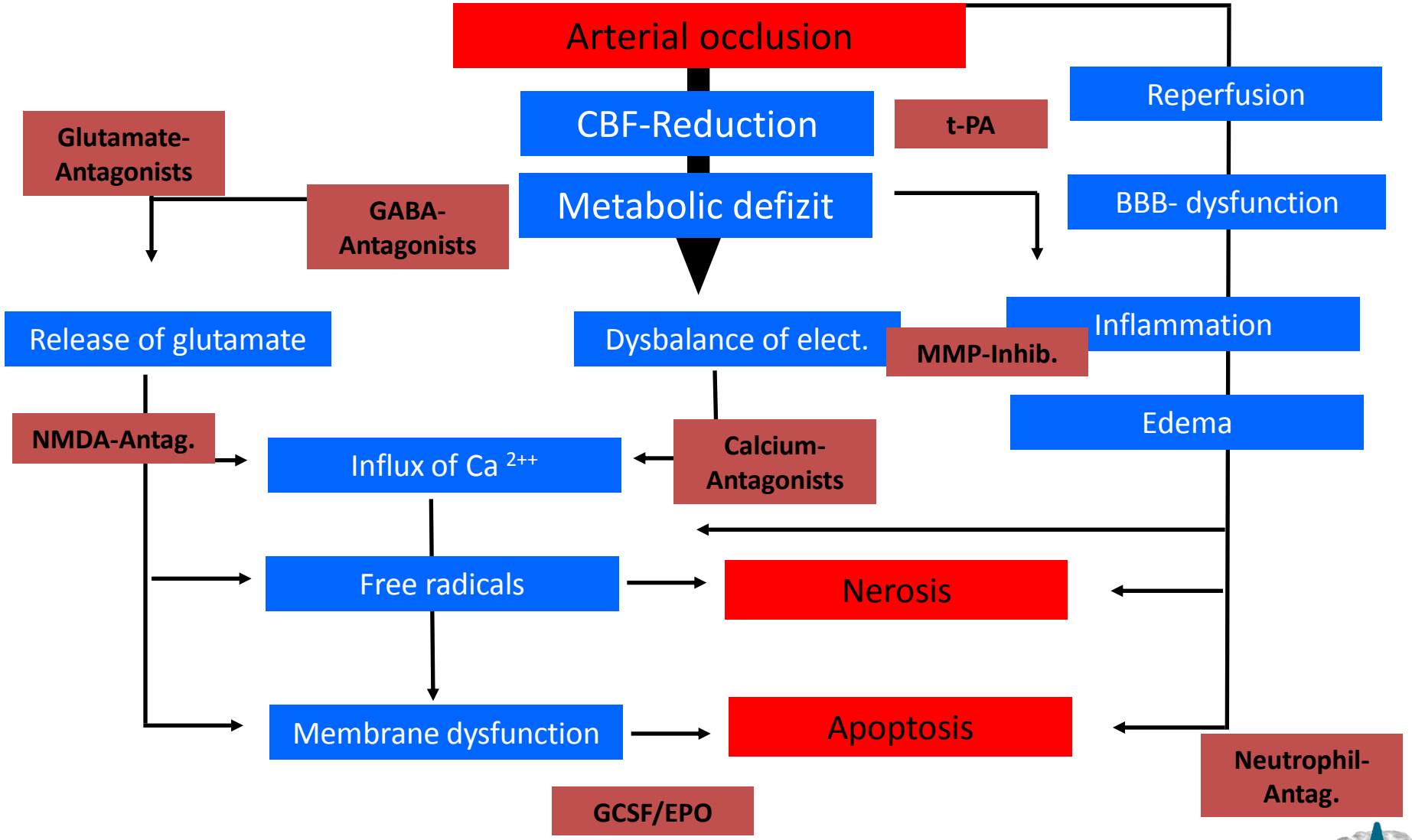
elevation ICP

ICP= intracranial pressure

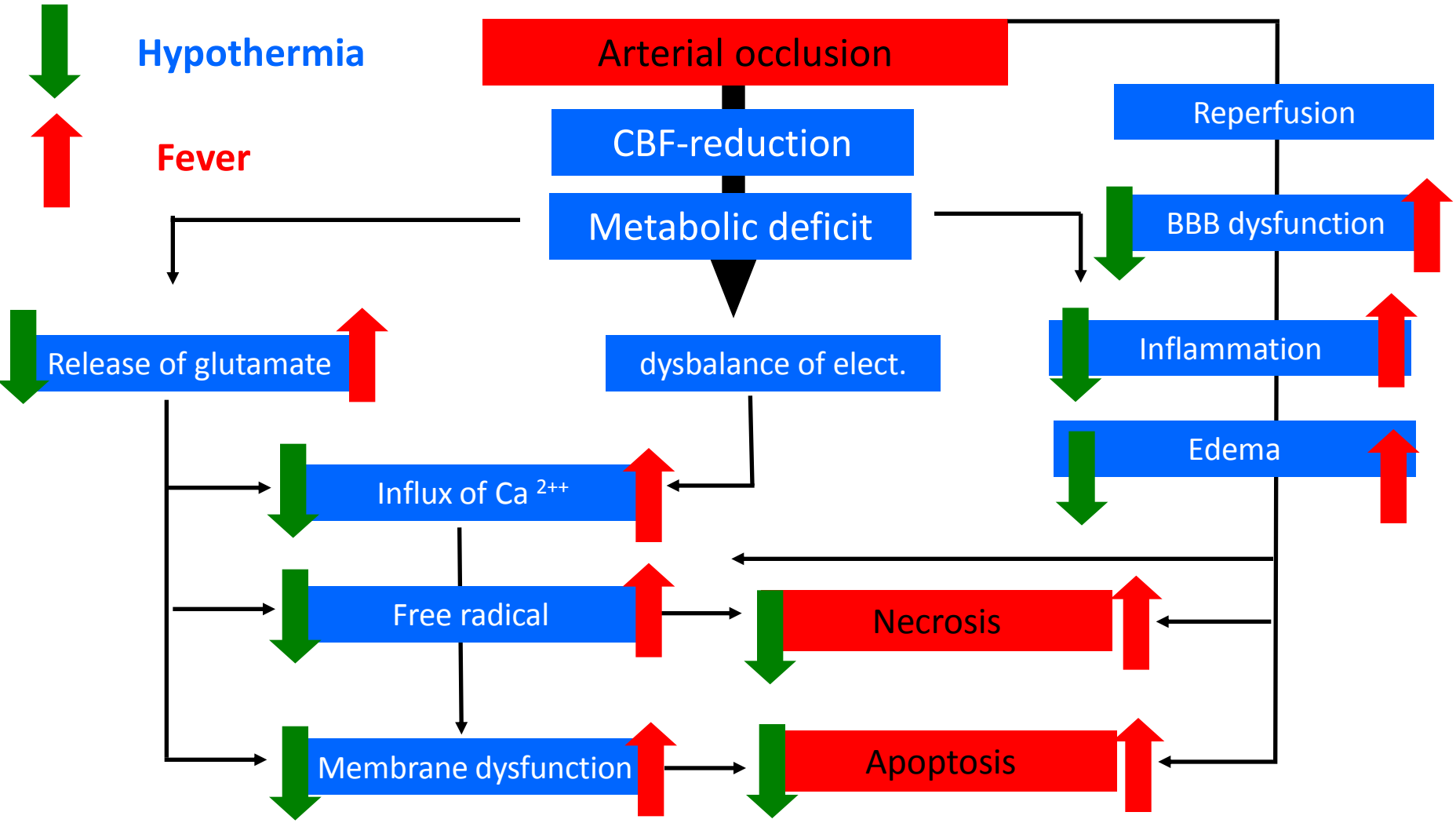
Pathophysiological mechanism induced by isch. Stroke:



Neuroprotection after Stroke:



Onsets of Hypothermia:



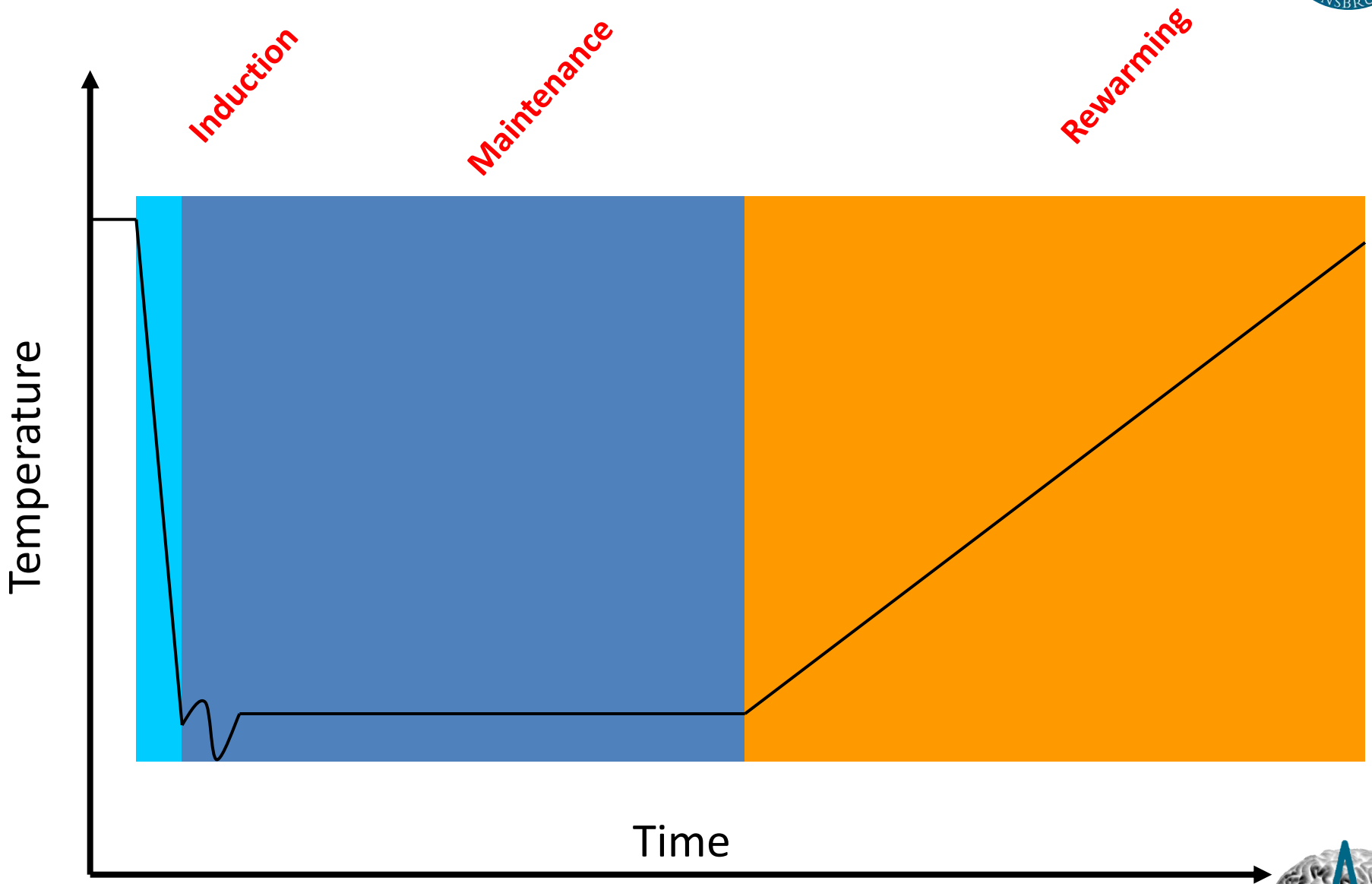
(Possible) indications for therapeutic hypothermia:

Comatose survivors after cardiac arrest
(refractory) Elevated intracranial pressure (ICP)
Asphyctic neonates
Hepatic encephalopathy
Heat stroke

Stroke
Traumatic brain injury
Myocardial infarction
Spinal cord injury
Status epilepticus
Meningitis

Evidence level

Phases of hypothermia:



Practical approach to hypothermia:

Pre-Induction:

avoid shivering through medication and counter warming

Induction:

as fast as possible (ice cold saline 4°C i.v., 30ml/kg /bw)
Target temperature 34° - 35°C (avoid overshoot)

Maintenance:

at least 24hrs (up to 7 days)
closely maintain target temperature (use devices – endovascular vs surface)

Rewarming:

very slow (!)
controlled rewarming (0.1 °C/hr)

Post rewarming:

avoid fever (close temperature surveillance)

Therapeutic temperature management requires:

continuous monitoring of:

body core temperature
cardiovascular functions
renal functions

standardized

surveillance of infections
laboratory work up
treatment of shivering

ICP monitoring

Limitations of Hypothermia :

LACK OF EFFECT OF INDUCTION OF HYPOTHERMIA AFTER ACUTE BRAIN INJURY

GUY L. CLIFTON, M.D., EMMY R. MILLER, PH.D., R.N., SUNG C. CHOI, PH.D., HARVEY S. LEVIN, PH.D., STEPHEN MCCAULEY, PH.D., KENNETH R. SMITH, JR., M.D., J. PAUL MUIZELAAR, M.D., PH.D., FRANKLIN C. WAGNER, JR., M.D., DONALD W. MARION, M.D., THOMAS G. LUERSSEN, M.D., RANDALL M. CHESNUT, M.D., AND MICHAEL SCHWARTZ, M.D.

NEJM, 2001

Very early hypothermia induction in patients with severe brain injury (the National Acute Brain Injury Study: Hypothermia II): a randomised trial

Guy L Clifton, Alex Valadka, David Zygun, Christopher S Coffey, Pamala Drever, Sierra Fourwinds, L Scott Janis, Elizabeth Wilde, Pauline Taylor, Kathy Harshman, Adam Conley, Ava Puccio, Harvey S Levin, Stephen R McCauley, Richard D Bucholz, Kenneth R Smith, John H Schmidt, James N Scott, Howard Yonas, David O Okonkwo

Lancet Neurology, 2010

Limitations – Infections:

Intravenous Thrombolysis Plus Hypothermia for Acute Treatment of Ischemic Stroke (ICTuS-L): Final Results

Table 3. Outcome Measures Between HY and NT Patients

	HY (Groups 2, 5, 6; n=28)	NT (Groups 1, 3, 4; n=30)	Fisher Exact Test *P*
mRS 0–1 at 90 days	5	7	0.747
NIHSS at 90 day (mean±SD)	6.3 (±6.6)	3.8 (±3.0)	0.355
At least one SAE (%)	75	43.3	0.018
Pneumonia (%)	50	10	0.001
All ICH (%)	28.6	20	0.752
Symptomatic ICH (%)	3.6	10	0.609
Mortality by 90 days (%)	21.4%	16.7	0.744

SAE indicates serious adverse event; ICH, intracerebral hemorrhage.

Hemmen et al., Stroke 2010

Controlled prophylactic normothermia

Concept of controlled prophylactic normothermia:

Negative effects of fever:

independent predictor of unfavorable outcome

breakdown of blood-brain-barrier

vascular permeability↑

– leads to brain edema

mitochondrial dysfunction

increased metabolic demand↑

free radicals↑

focal hyperthermia „Thermopooling“↑

Reperfusion Injury ↑

Broessner 2009, Diringer 2005, Polderman 2004, Polderman 2008, Child 2005, Rumana 1998, Clifton 2001

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mitochondrial dysfunction

increased metabolic demand↑

free radicals↑

focal hyperthermia „Thermopooling“↑

Reperfusion Injury ↑

Negative effects of hypothermia:

Hypotonia (TBI)

Infectious complications

Magnesium

Sodium

Shivering

Rewarming Injury *(„rebound effect“)*

„awake patient“

reduction of rTPA action (?)

Broessner 2009, Diringer 2005, Polderman 2004, Polderman 2008, Child 2005, Rumana 1998, Clifton 2001

Concept of controlled prophylactic normothermia:

Negative effects of fever:

independent predictor of unfavorable outcome

br[illegible] of blood brain barrier

free radicals ↑

focal hyperthermia „Thermopooling“ ↑

Reperfusion Injury ↑

Negative effects of hypothermia:

Hypotonia (TBI)

„awake patient“

reduction of rTPA action (?)

controlled normothermia (36,5°C)

avoidance of the NEGATIVE effects of fever

WITHOUT incresing risk by hypothermia

Broessner 2009, Diringer 2005, Polderman 2004, Polderman 2008, Child 2005, Rumana 1998, Clifton 2001

Cerebrovascular diseases – Normothermia I

Prophylactic, Endovascularly Based, Long-Term Normothermia in ICU Patients With Severe Cerebrovascular Disease: Bicenter Prospective, Randomized Trial

Gregor Broessner, Ronny Beer, Peter Lackner, Raimund Helbok, Marlene Fischer, Bettina Pfausler, Janelle Rhorer, Lea Küppers-Tiedt, Dietmar Schneider and Erich Schmutzhard

Stroke A

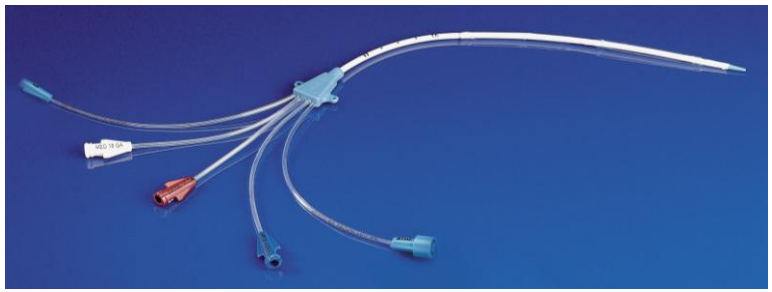
Journal of the American Heart Association

SAH HH 3-5
ICH GCS ≤ 10
Stroke NiHSS ≥ 15

36,5°C

A

CoolGard 3000, Zoll Corp.



B

conventional
„ controls „

Temp > 37,9°C

conventional temperature management treatment, stepwise escalating

1. Paracetamol 500mg p.o.
2. Naproxen 500mg p.o.
3. Pethidin 100mg i.v.
4. ICE packs
5. Cool „washing“
6. cooling balnkets (Blanketrol®)

Broessner et. al., Stroke 2009

Cerebrovascular diseases – Normothermia II

Baseline Variable	CoolGard (n=51)	Control (n=51)	*P* Value	
Cerebrovascular disease, n (%)			0.60	
CI	4 (8)	6 (12)		168 hrs
ICH	19 (37)	22 (43)		
SAH	28 (55)	23 (45)		336 hrs

Broessner et. al., Stroke 2009

Primary Outcome

	Total Fever Burden in Hours (AUC)		
Disease Category	CoolGard (n=51)	Control (n=51)	*P* Value
Overall			<0.0001
No.	51	51	
Mean±SD	1.5±3.3	9.3±14.5	
Median	0.0	4.3	

Broessner et. al., Stroke 2009

Sekondary Outcome (AE)

Table 2. Any Adverse Event by Infection Status

	Through Neuro-ICU Discharge			Through Day 30			Through Month 6		
Infection Type	CoolGard n (%)	Control n (%)	*P* Value	CoolGard n (%)	Control n (%)	*P* Value	CoolGard n (%)	Control n (%)	*P* Value
Overall	48 (94)	43 (84)	0.20	49 (96)	44 (86)	0.16	49 (96)	44 (86)	0.16
Infectious	48 (94)	40 (78)	0.04	49 (96)	41 (80)	0.03	49 (96)	41 (80)	0.03
Noninfectious	19 (37)	20 (39)	1.00	19 (37)	20 (39)	1.00	19 (37)	20 (39)	1.00

Broessner et. al., Stroke 2009

Tertiary Outcome

Table 5. Neurologic Function

	Discharge		Day 30		Month 6	
	CoolGard n (%)	Control n (%)	CoolGard n (%)	Control n (%)	CoolGard n (%)	Control n (%)
GOS						
Death	9 (18)	8 (16)	12 (24)	10 (20)	18 (35)	14 (27)
Persistent vegetative state	6 (12)	7 (14)	3 (6)	4 (8)	0	3 (6)
Severe disability	25 (49)	24 (47)	21 (41)	21 (41)	9 (18)	9 (18)
Moderate disability	8 (16)	7 (14)	7 (14)	6 (12)	8 (16)	9 (18)
Good recovery	3 (6)	5 (10)	2 (4)	5 (10)	9 (18)	12 (24)
Intubated	0	0	3 (6)	1 (2)	0	0
Lost to follow-up	0	0	2 (4)	1 (2)	7 (14)	4 (8)
Missing	0	0	1 (2)	3 (6)	0	0
P value	0.81		0.55		0.41	

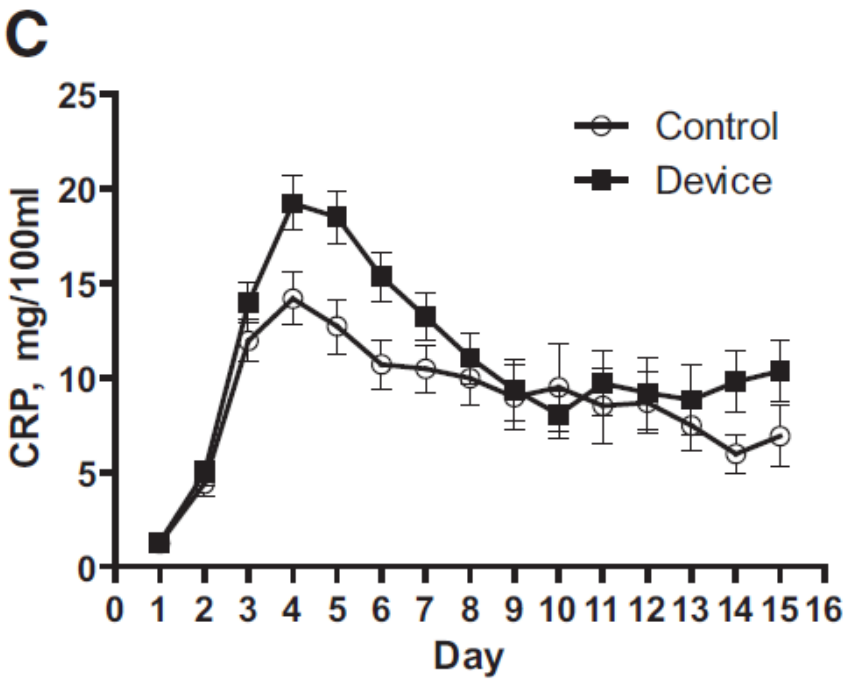
Broessner et. al., Stroke 2009

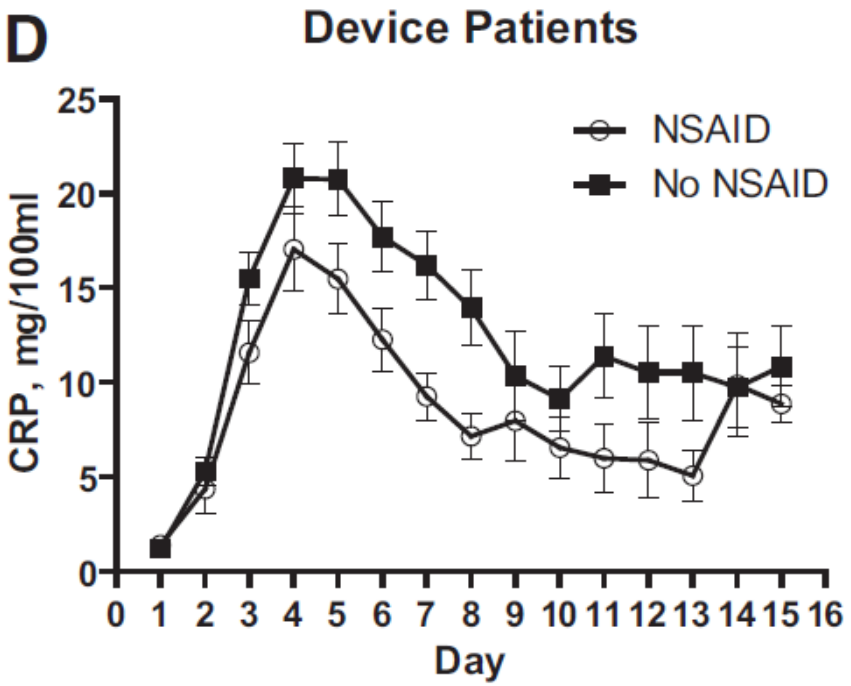
Rate of infectious complications vs. inflammatory parameters?

Baseline Variable	CoolGard (n=51)	Control (n=51)	*P*
Longitudinal data of inflammatory parameters			
C-reactive protein, mg/100 mL (mean±SD)	10.8±6.0	8.6±5.6	0.03
WBCs, G cells/L (mean±SD)	10.3±3.3	10.5±2.8	0.84
IL-10, pg/mL (mean±SD)	11.3±17.2	10.9±16.5	0.72
IL-6, pg/mL (mean±SD)	95.2±82.2	72.7±83.8	0.03
Procalcitonin, μg/L (mean±SD)	0.4±1.1	0.7±1.4	0.60

Broessner & Schmutzhard et al., Stroke 2010

Cerebrovascular diseases – Normothermie V





Broessner & Schmutzhard et al., Stroke 2010

Cerebrovascular diseases – Normothermie V

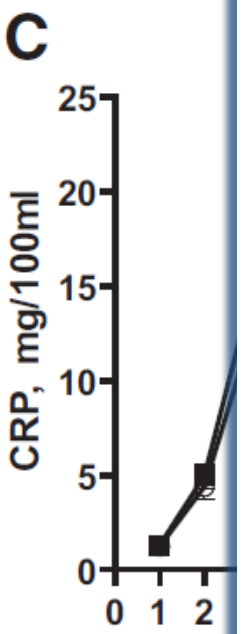
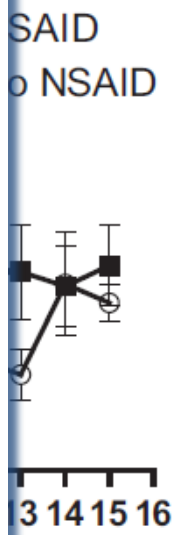


Table 2. Predictors of Unfavorable Neurologic Long-Term Outcome

Parameter	Odds Ratio	95% Confidence Interval		*P*
Age	1.09	1.04	1.13	<0.001
Endovascular group		Reference Category		
Control group	1.56	0.5	4.88	0.44
No NSAID		Reference Category		
NSAID applied	0.36	0.1	1.24	0.1
LOS neuro-ICU	1.01	0.99	1.04	0.35
Sex	0.58	0.2	1.68	0.31



Unfavorable outcome MRS 3-6

Broessner & Schmutzhard et al., Stroke 2010

Normothermia and TBI I:

Induced Normothermia Attenuates Intracranial Hypertension and Reduces Fever Burden after Severe Traumatic Brain Injury

severe TBI GCS ≤ 8

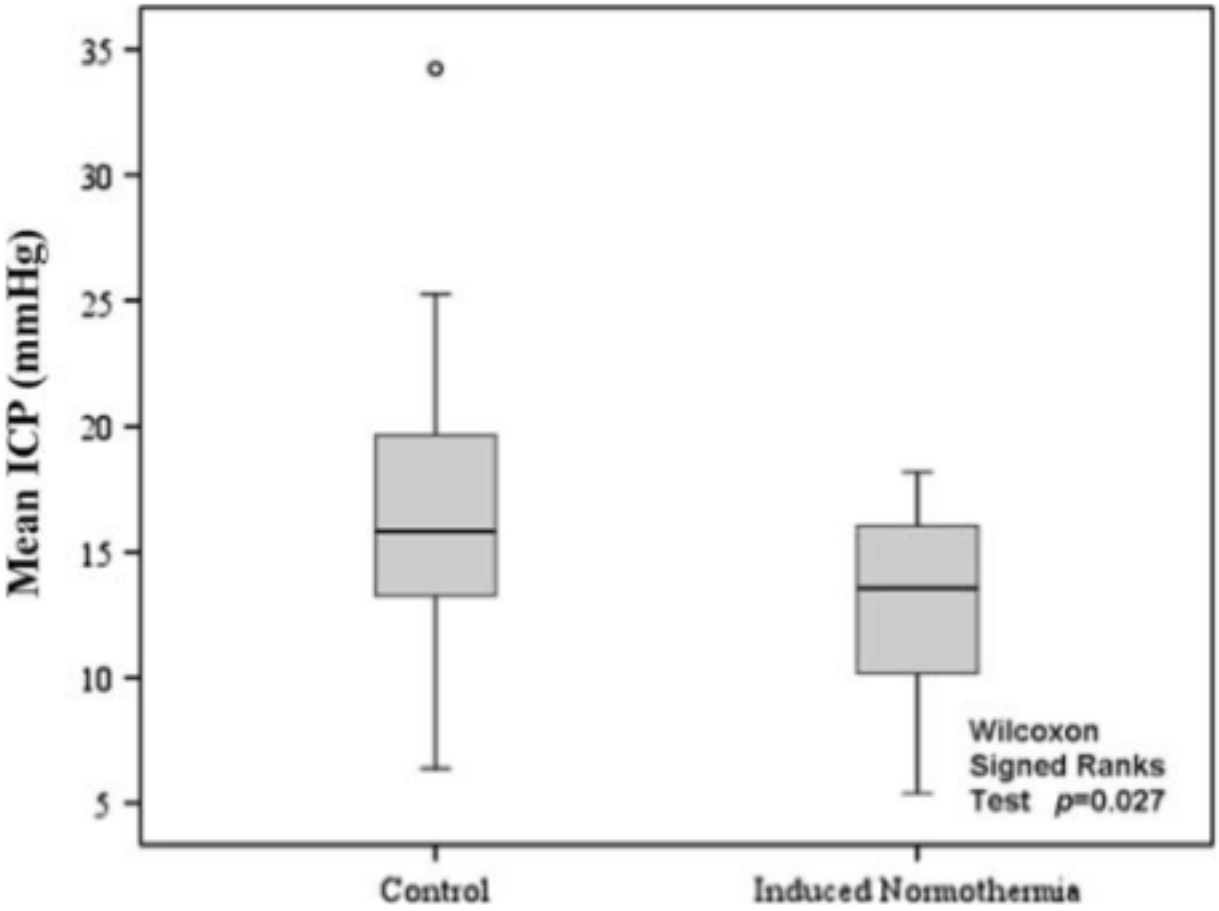
N= 21 patients
endovaskular normothermia (TT 36 – 36,5°C)
(Zoll®, Coolgard®) over 36 hrs

comparison with „historic controls“ (N=21)

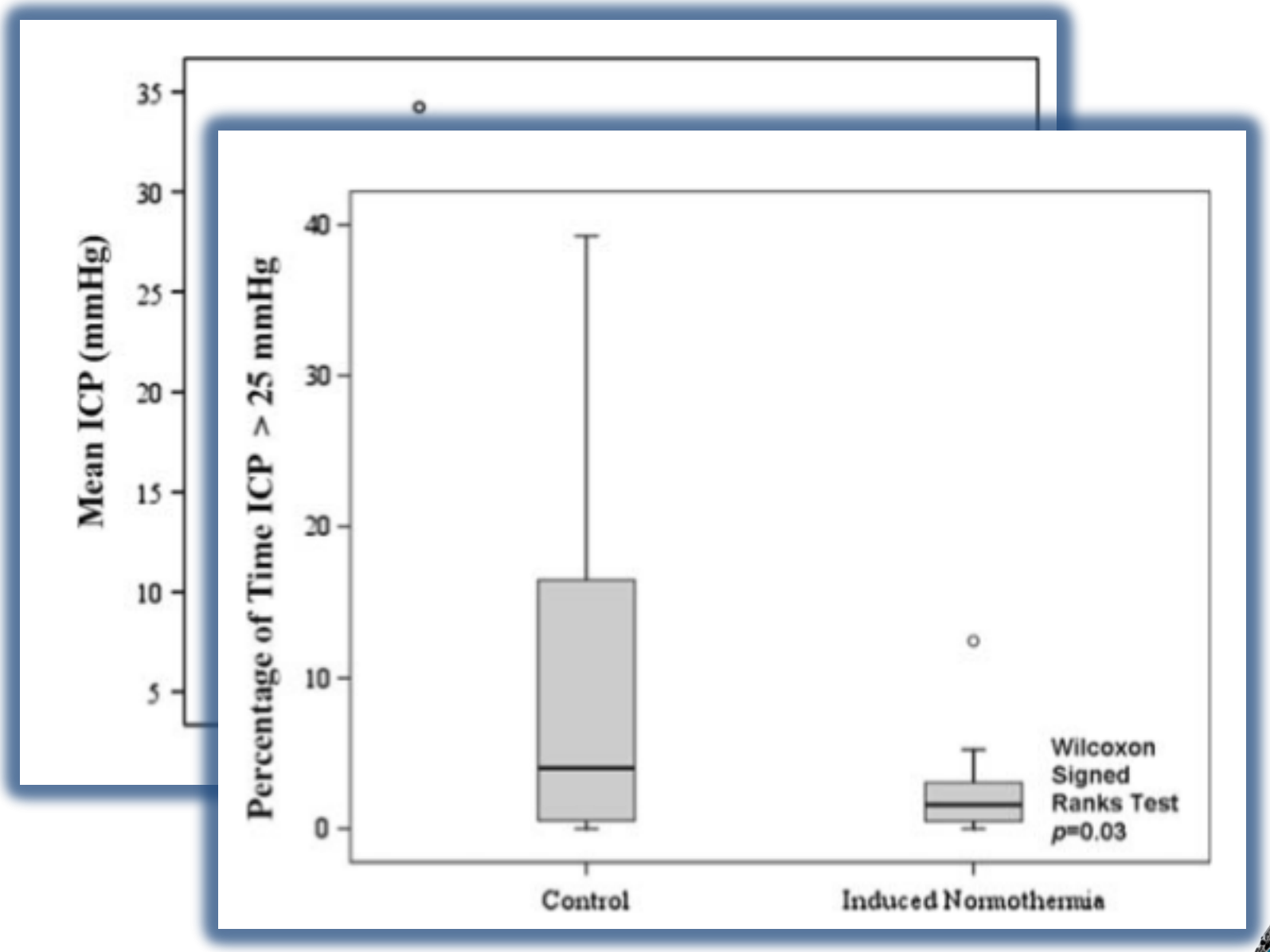
ICP monitoring *(Licox®)*

Puccio et al., Neuro Crit Care 2009

Normothermia and TBI iI:



Normothermia and TBI iI:



Therapeutic hypothermia

TBI – measurment of brain temperature

Can prophylactic endovascular normo-/hypothermia influence brain temperature (in patients with severe TBI)?

Inclusion criteria:

severe TBI (intial GCS ≤ 8)

Interventions:

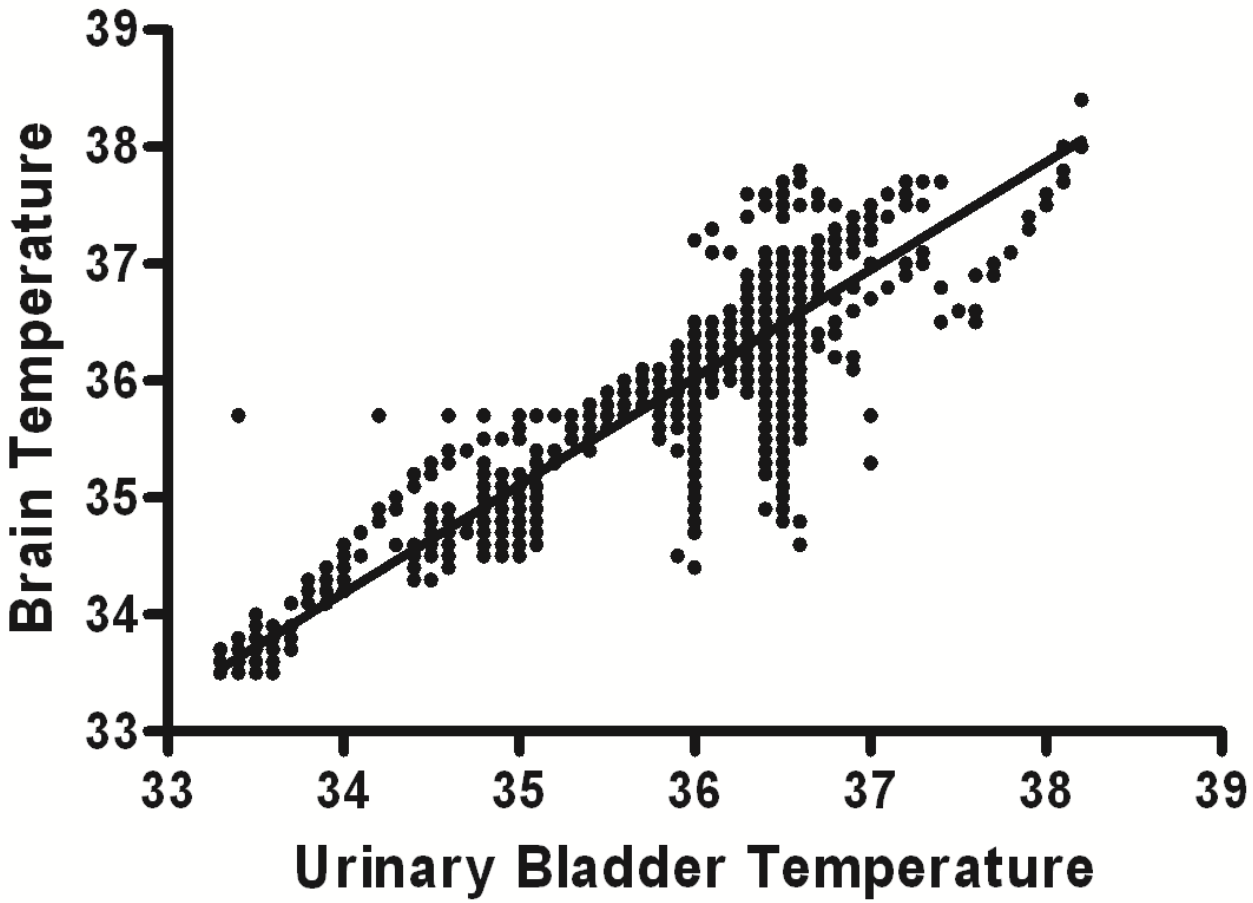
ICP + temperatureprobe (Neurovent-Temp-P, Raumedic AG, Muenchberg, Germany)
endovascular normo/ hypothermia (CoolGard 3000®, Zoll®)

N=7 patients

Fischer & Broessner et al., Neurosurgery 2011

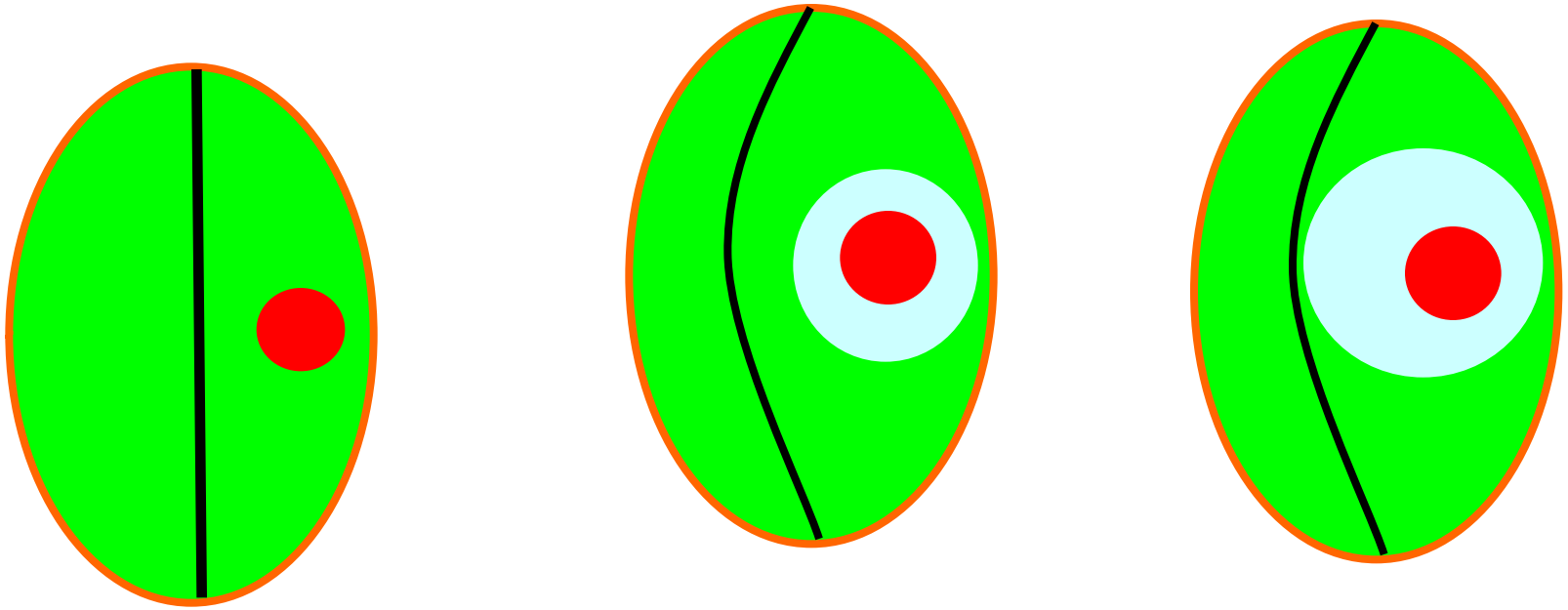
TBI – brain versus bladdertemperature under normo/hypothermia

CC r= 95

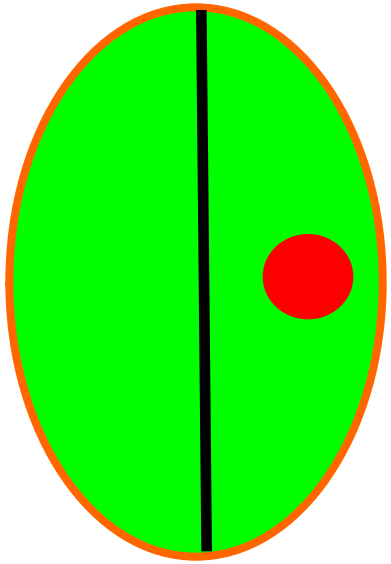


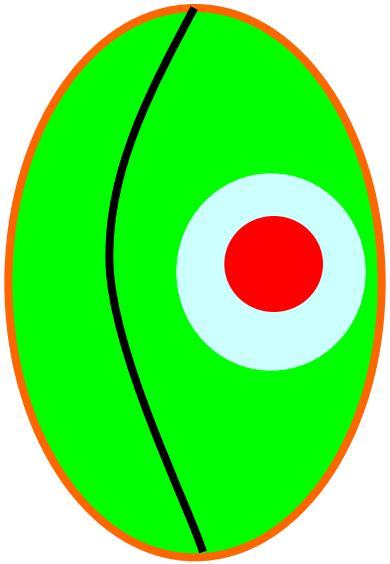
Fischer & Broessner et al., Neurosurgery 2011

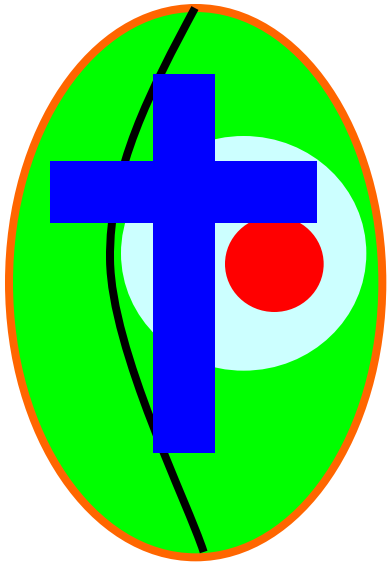
Hypothermia and ICH:



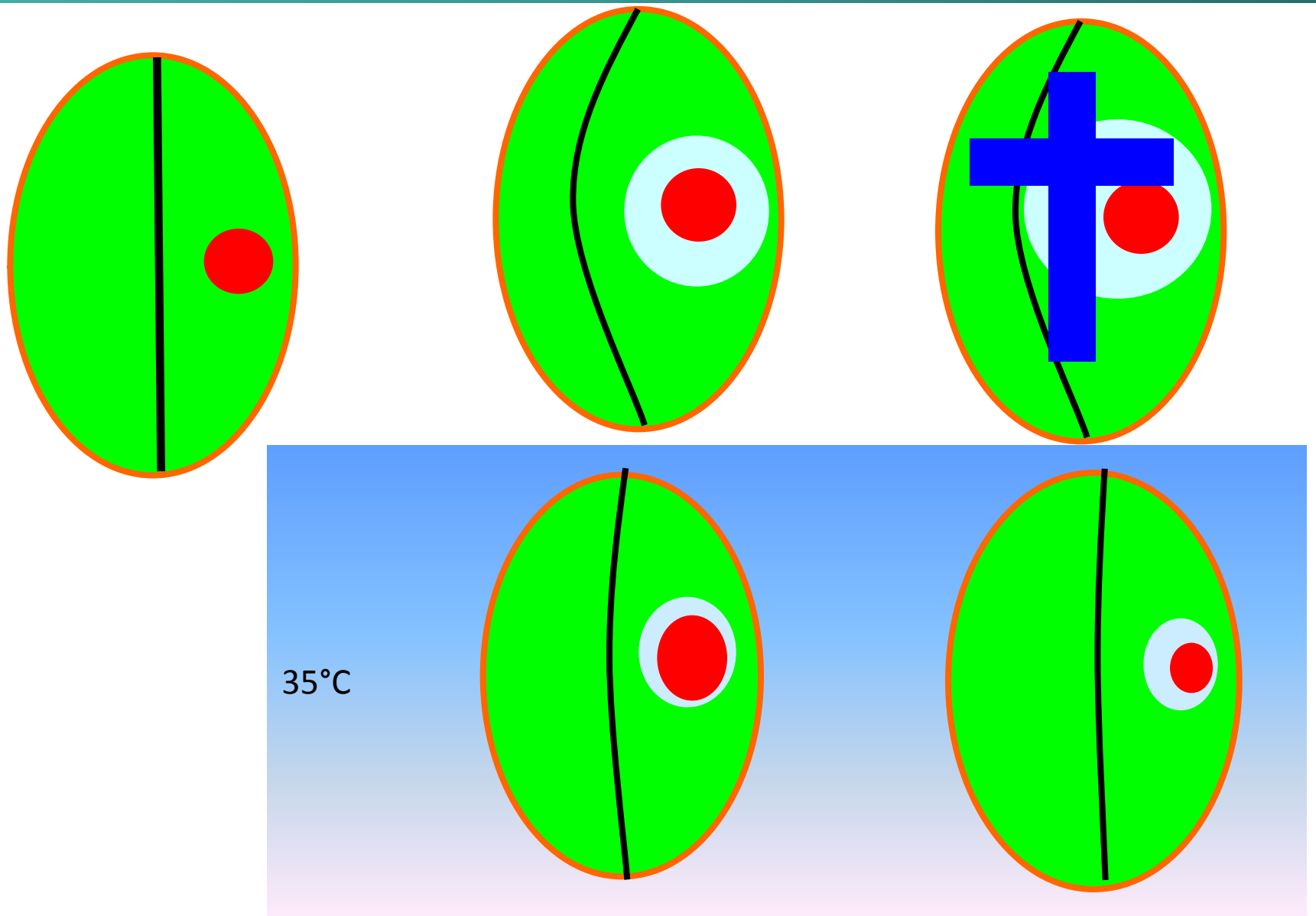
Hypothermia and ICH:







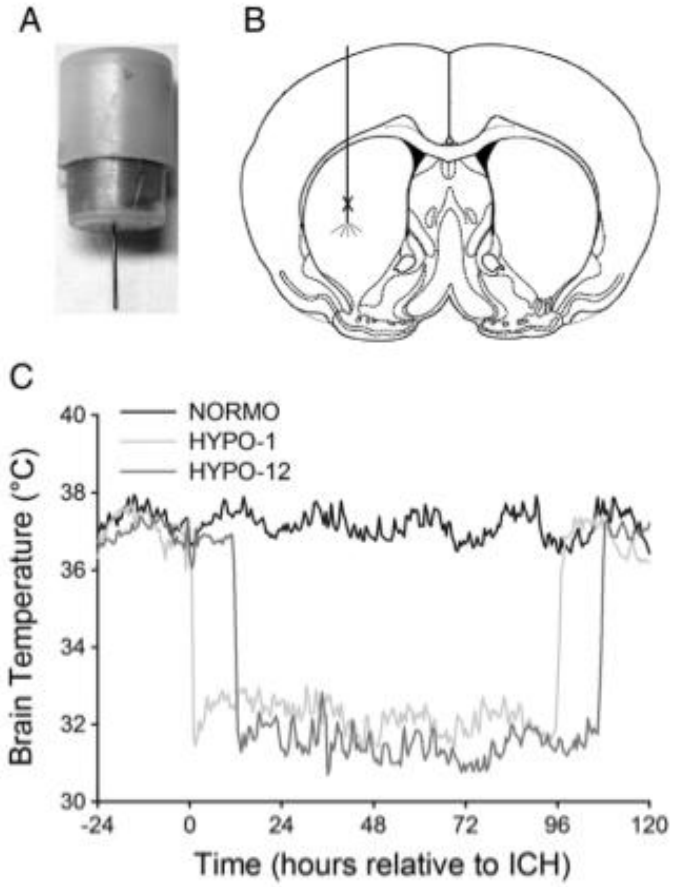
Hypothermia and ICH:



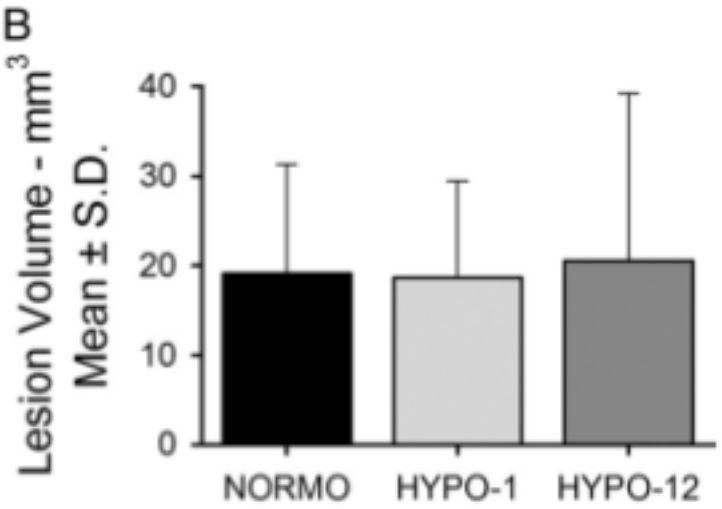
Hypothermia in ICH rat model:

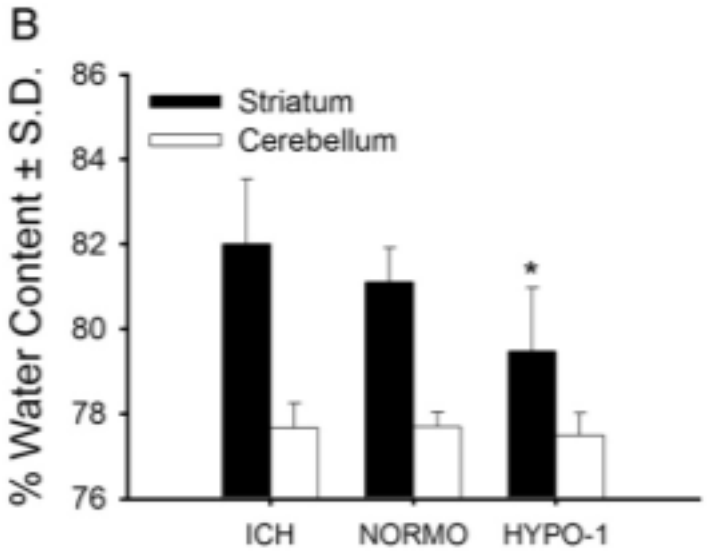
The effects of selective brain hypothermia on intracerebral hemorrhage in rats

Matthew Fingas [a], Darren L. Clark [a], Frederick Colbourne [a,b,*]



Hypothermia in ICH rat model:





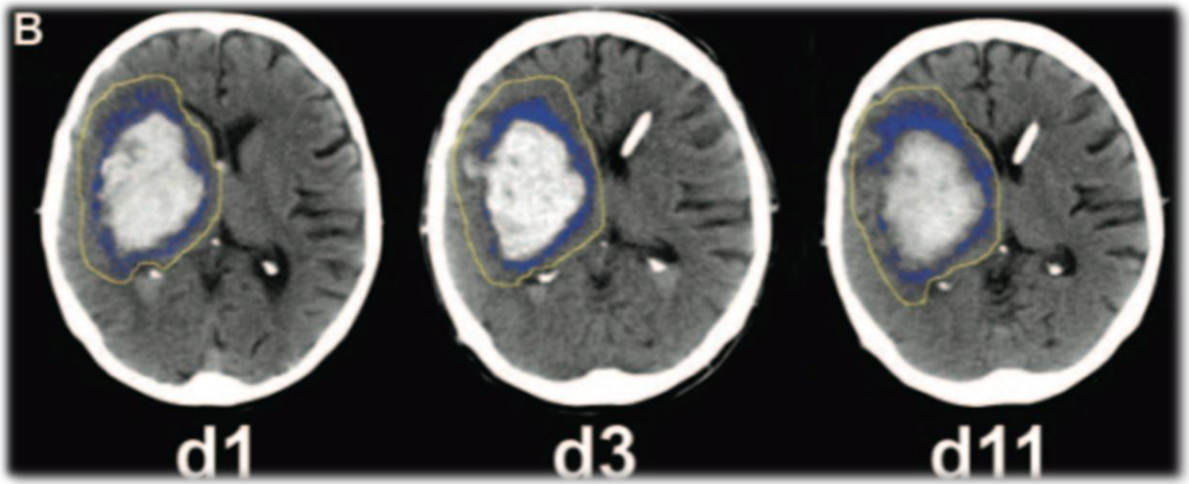
Hypothermia and ICH:

Hypothermia Reduces Perihemorrhagic Edema After Intracerebral Hemorrhage

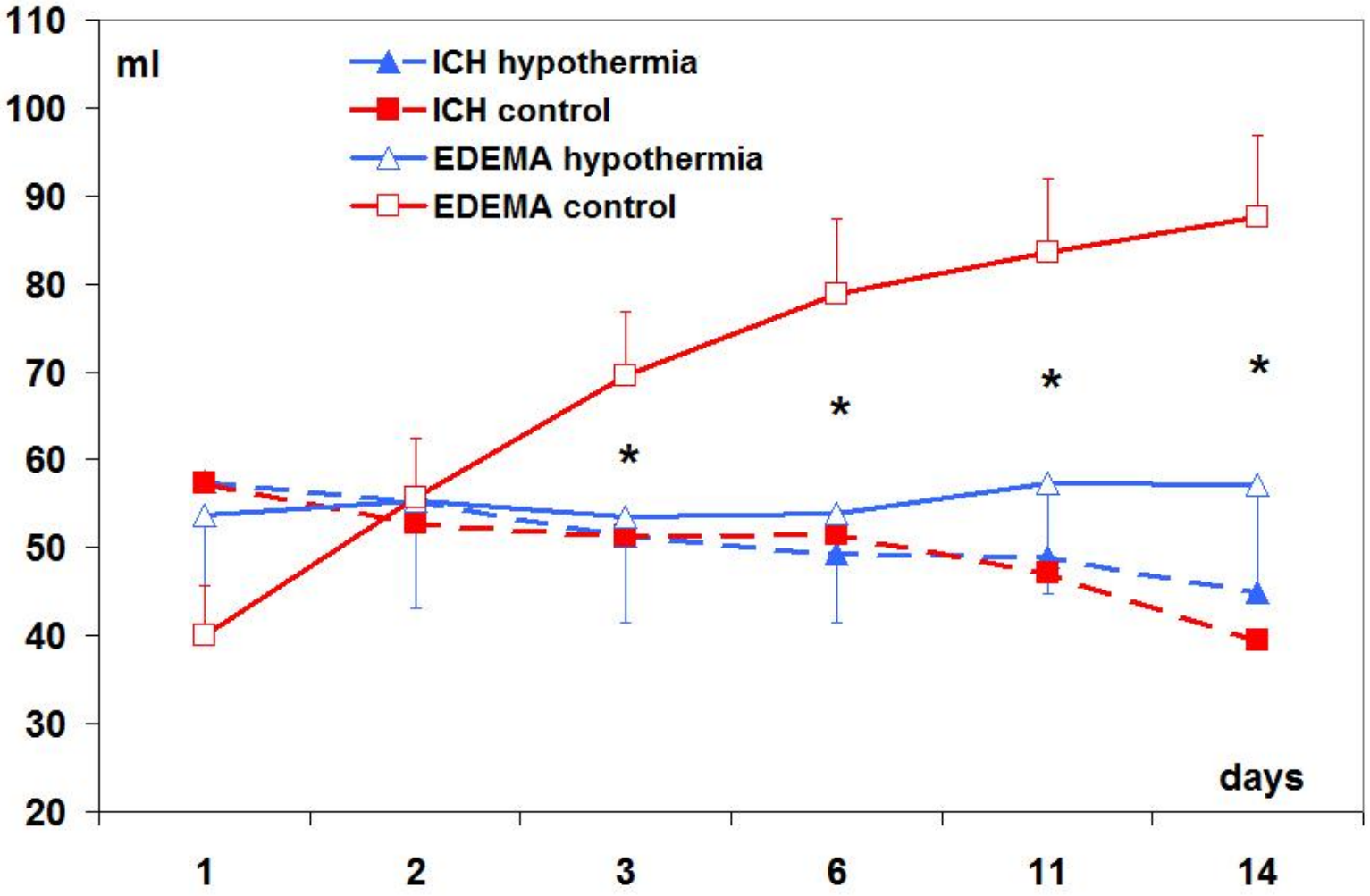
Rainer Kollmar, Dimitre Staykov, Arnd Dörfler, Peter D. Schellinger, Stefan Schwab and Jürgen Bardutzky

Normo / Hypothermia over 10 days

Hypothermia (n=12)	Control (n=25)



Hypothermia and ICH :



Kollmar, Staykov et al., Stroke 2010

Ongoing trials with temperature management

Clinicaltrials.gov (National Institutes of Health (NIH))

Hypothermia:

78 registered trials (recuiting or before recruiting)

Indications: Stroke, bact. meningitis, status epilepticus, TBI, SAH, cardiac arrest, asphyxia a.m.m.

Controlled normothermia:

9 registered trials (recuiting or before recruiting)

Ongoing trials with temperature management:

Cooling in intracerebral hemorrhage (CINCH) trial: protocol of a randomized German–Austrian clinical trial

Rainer Kollmar[1]*, Eric Juettler[2], Hagen B. Huttner[1], Arnd Dörfler[3], Dimitre Staykov[1], Bernd Kallmuenzer[1], Erich Schmutzhard[4], Stefan Schwab[1], Gregor Broessner[4]
for the CINCH investigators

Ongoing trials with temperature management:

ICTuS-2/3

Intravenous Thrombolysis Plus Hypothermia for Acute Treatment of Ischemic Stroke-2/3

Ongoing trials with temperature management :

EXTENDED SYNPOSIS

EuroHYP-1: A European, multicentre, randomised, phase III, clinical trial of hypothermia plus medical treatment versus best medical treatment alone for acute ischaemic stroke

Summary I:

fever has to be ***avioded in patients with acute neuronal injury*** by any means

Good evidence for hypothermia (RCT):

Post resuscitation
Refractory elevated ICP
Asphyctic neonates

promising results in Stroke, ICH....

(***longterm-) prophylactic endovasacular normothermia*** is ***efficacious*** and ***feasibel***

Summary II:

Understanding and ***treating the limitations*** in therapeutic temprature management is pivotal:

(even under prophylactic normothermia) close and ***standardized surveillance*** for ***infections*** is absolutely mandatory – treatment of fever does ***not replace treatment of infections***

use anti-shivering protocol

avoid fever rebound

Сердечное спасибо!