4th Innsbruck/Berlin Targeted Temperature Management Symposium

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November 20-21, 2015
Berlin, Germany

MEETING ABSTRACTS

Congress Presidents:
Christian Storm, Berlin GER
Erich Schmutzhard, Innsbruck, A
Gregor Brössner, Innsbruck, A

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Invited Speakers

Peter Andrews, MD
Professor of Anaesthesia
Centre for Clinical Brain Sciences
University of Edinburgh & Lothian University Hospitals
EH42XU Edinburgh, United Kingdom
Email: p.andrews@ed.ac.uk

Neeraj Badjatia, MD
Professor of Neurology
Department of Neurology
University of Maryland Medical Center
Baltimore, MD 21201-1595, USA
Email: nbadjatia@som.umaryland.edu

Wilhelm Behringer, MD
Professor of Emergency Medicine
Department of Emergency Medicine
Medical University of Vienna
A-1090 Vienna, Austria
Email: wilhelm.behringer@meduniwien.ac.at

Julian Bösel, MD
Neurocritical Care Unit
Department of Neurology
University of Heidelberg
69120 Heidelberg, Germany
Email: julian.boesel@med.uni-heidelberg.de

Bernd Böttiger, MD
Professor of Anaesthesia
Department of Anaesthesiology and Intensive Care Medicine
University Hospital of Cologne
D-50937 Cologne, Germany
Email: bernd.boettiger@uk-koeln.de

Gregor Brössner, MD
Associate Professor of Neurology
Department of Neurology
Medical University Innsbruck
A-6020 Innsbruck, Austria
Email: gregor.broessner@i-med.ac.at

Invited Speakers

W. Dalton Dietrich, MD, PhD
Scientific Director, The Miami Project to Cure Paralysis
Kinetic Concepts Distinguished Chair in Neurosurgery
Senior Associate Dean for Discovery Science
Professor of Neurological Surgery, Neurology and
Cell Biology and Anatomy
University of Miami, Leonard M. Miller School of Medicine
Lois Pope LIFE Center
1095 NW 14th Terrace, Suite 2-30, Miami, FL 33136-1060, USA
Email: ddietrich@miami.edu

David Erlinge, MD
Professor of Cardiology
Department of Cardiology
Lund University Skåne University Hospital
Lund, Sweden
Email: David.Erlinge@med.lu.se

Markus Födisch, MD
Department of Anaesthesiology, Intensive Care & Emergency Medicine
Waldkrankenhaus Bonn
D-53177 Bonn, Germany
Email: markus.foedisch@ek-bonn.de

Norbert Frey, MD
Professor of Cardiology
Clinic for Cardiology and Angiology
Universitätsklinikum Schleswig-Holstein
D-24105 Kiel, Germany
Email: norbert.frey@uk-sh.de

Michael Fries, MD
Assistant Professor of Anaesthesia
Department of Anaesthesiology and Intensive Care Medicine
St.-Vincenz Hospital Limburg
D-66549 Limburg, Germany
Email: m.fries@st-vincenz.de

David Greer, MD, MA
Professor of Neurology and Neurosurgery
Vice Chairman, Department of Neurology
Dr. Harry M. Zimmerman and Dr. Nicholas and Viola Spinelli Endowed Chair
Director, Stroke Service
Director of Medical Studies
Yale University School of Medicine
New Haven, CT 06520-8018, USA
Email: david.greer@yale.edu

Invited Speakers

Raimund Helbok, MD
Department of Neurology
Medical University Innsbruck
A-6020 Innsbruck, Austria
Email: raimund.helbok@uki.at

Rob Henning, MD
Professor of Pharmacology
Faculty of Medical Sciences, Clinical pharmacy & pharmacology
University of Groningen
9713 GZ Groningen, The Netherlands
Email: r.h.henning@umcg.nl

Emanuela Keller, MD
Neurointensive Care Unit, Department of Neurosurgery
University Hospital Zurich
CH-8091 Zürich, Switzerland
Email: emanuela.keller@usz.ch

Christoph Leithner, MD
Department of Neurology
Charité - Universitätsmedizin Berlin
D-13353 Berlin, Germany
Email: christoph.leithner@charite.de

Peter Paal, MD
Associate Professor
Department of Anesthesiology and Critical Care Medicine
Medical University Innsbruck
A-6020 Innsbruck, Austria
Email: Peter.Paal@uki.at

Barts Heart Centre, St Bartholomew's Hospital, West Smithfield, London, EC1A 7BE, Barts Health NHS Trust, Queen Mary University of London, United Kingdom

Kees Polderman, MD
Department of Critical Care Medicine
University of Pittsburgh
Pittsburgh, PA 15261, USA
Email: poldermankh@upmc.edu

Jonathan Rhodes, MD
Department of Anaesthesia, Critical Care & Pain Medicine
University of Edinburgh Western General Hospital
EH4 2XU Edinburgh, United Kingdom
Email: jrhodes1@staffmail.ed.ac.uk

Invited Speakers

Fred Rincon, MD
Assistant Professor of Neurology
Department of Neurology
Thomas Jefferson University Hospital
Philadelphia, PA 19107, USA
Email: fred.rincon@jefferson.edu

Erich Schmutzhard, MD
Professor of Neurology and Critical Care Medicine
Department of Neurology
Medical University Innsbruck
A-6020 Innsbruck, Austria
Email: erich.schmutzhard@i-med.ac.at

Stefan Schwab, MD
Professor of Neurology
Director of the Department of Neurology
University Hospital Erlangen
D-91054 Erlangen, Germany
Email: stefan.schwab@uk-erlangen.de

Mathias Stöckl, MD
Department of Emergency Medicine
Medical University of Vienna
A-1090 Vienna, Austria
Email: mathias.stoeckl@meduniwien.ac.at

Christian Storm, MD
Department of Nephrology and Intensive Care
Charité University Berlin
D-13353 Berlin, Germany
Email: christian.storm@charite.de

Tobias Welte, MD
Professor of Pneumology
Department of Respiratory Medicine
Hannover Medical School
D-30625 Hannover, Germany
Email: welte.tobias@mh-hannover.de

November 20, 2015

Session 1:	TTM in Cardiac Arrest
08.45 - 09.30	Key Note Lecture: Temperature management after cardiac arrest (out of and in hospital) New Guidelines and recommendations (ERC, AHA) Bernd Böttiger, Cologne (DE)

Surviving cardiac arrest requires more than cardiopulmonary resuscitation (CPR). Following return of spontaneous circulation (ROSC), the so called post cardiac arrest syndrome evolves, consisting of neuronal injury, myocardial dysfunction and systemic inflammation. Targeted temperature management is considered a key to reducing mortality and morbidity after cardiac arrest.

In 2002, two randomised clinical trials showed that therapeutic hypothermia of 32–34 °C for 12–24 hours improved outcome after out-of-hospital cardiac arrest due to ventricular fibrillation (1, 2).

More recently, the Targeted Temperature Management (TTM) trial investigated temperature control to 33 or 36 °C for 24 hours in patients after out-of-hospital cardiac arrest regardless of initial ECG rhythm (3). Following rewarming, temperature was kept < 37.5 °C for 72 hours in both groups. There were no differences in survival and neurologic outcome and neither in side effects. Remarkably, 73 % of the patients in this study had received bystander CPR, and the median no-flow time in both groups was one minute.

In paediatric cardiac arrest, a randomised clinical trial showed a trend towards improved survival with good neurologic outcome by hypothermia of 33 °C for 48 hours compared to 36.8 °C (4). This did not reach statistical significance, probably because the study was underpowered.

Several non-randomised studies draw attention on avoiding fever, which is a common complication after cardiac arrest – in the beginning and still after a period of therapeutic hypothermia (5, 6).

In conclusion, all patients require prolonged targeted temperature management after cardiac arrest. Following ROSC, unconscious patients should receive therapeutic hypothermia of 32–34 °C for 24 hours. Particularly after very short periods of no-flow time, 36 °C may also be effective. Rewarming must be performed slowly, and fever should be avoided during the following days.

Hypothermia can be induced by various methods such as ice packs, cooling pads, air circulating blankets, cold infusions, intravascular cooling catheters or trans-nasal evaporative cooling. None of these means has proven superior. However, high volumes of ice cold infusions should be avoided or used with caution.

While a certain amount of fluids is usually needed for ensuring adequate circulation, over-dosing can result in pulmonary oedema and even cardiac re-arrest (7).

Targeted temperature management should be included into a treatment bundle which also consists of early coronary interventions (if indicated) and goal-directed therapy (normotension, normoglycaemia, normocapnia, normoxaemia). According to the recent advisory statement of the European Resuscitation Council and the European Society of Intensive Care Medicine, prognostication after cardiac arrest should not be performed earlier than 72 hours after ROSC.

1. Hypothermia after Cardiac Arrest Study Group. N Engl J Med 2002; 346: 549-556

2. Bernard et al. N Engl J Med 2002; 346: 557-563

3. Nielsen et al. N Engl J Med 2013; 369: 2197-2206

4. Moler et al. N Engl J Med 2015; 372: 1898-1908

5. Bro-Jeppesen et al. Resuscitation 2013; 84: 1734-1740

6. Leary et al. Resuscitation 2013; 84: 1056-1061

7. Kim et al. JAMA 2014; 311: 45-52Eurotherm3235Trial

November 20, 2015

Session 1:	TTM in Cardiac Arrest
08.45 - 09.30	Key Note Lecture: Temperature management after cardiac arrest (out of and in hospital) New Guidelines and recommendations (ERC, AHA) Bernd Böttiger, Cologne (DE)

November 20, 2015

Session 1:	TTM in Cardiac Arrest
10.00 - 10.30	Cardiac arrest: TTM - time matters - best moment to start? David Erlinge, Lund (SE)

Hypothermia is an established treatment after cardiac arrest to protect against cerebral injury. Here it is discussed if hypothermia can also be used to protect the heart during ischemia induced by ST-elevation myocardial infarction (STEMI). Mild hypothermia (32-35° C) may be of benefit as adjunctive treatment for STEMI by having positive effects during ischemia to reduce infarct size and on the four components of ischemia reperfusion injury: myocardial stunning, microvascular obstruction, reperfusion arrhythmias and lethal reperfusion injury. In the treatment to reduce cerebral injury after cardiac arrest hypothermia can be initiated after reperfusion and should be maintained for 24-48 h. In contrast, for heart protection evidence suggests that hypothermia should be initiated as early as possible during ischemia, at least before reperfusion. Clinical and experimental results indicate that reaching a temperature of less than 35°C before reperfusion is of paramount importance in order to reduce infarct size in the treatment of STEMI patients. Treatment after reperfusion can be relatively short. Hypothermia has wide-ranging effects on most of the mechanisms involved in ischemia and reperfusion injury which may explain the potent, highly reproducible cardioprotective effects seen in a large number of studies in different species. Cooling awake patients with STEMI is safe, feasible and well tolerated, but anti-shivering strategies must be used.

The TTM study examined two levels of therapeutic hypothermia (33 vs 36°) for the treatment of out of hospital cardiac arrest in 939 patients. It is one of the largest randomized clinical trials in cardiac arrest and by far the largest on therapeutic hypothermia for cardiac arrest. It is therefore interesting to examine the study results for secondary endpoints. In the talks, the importance of time to target temperature for the outcome of cardiac arrest will be analysed. Furthermore, a possible cardioprotective effect of 33° will be examined in TTM especially In patients with STEMI and NSTEMI.

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10.00 - 10.30	Cardiac arrest: TTM - time matters - best moment to start? David Erlinge, Lund (SE)

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Session 2:	TTM in cardiac diseases and non-cardiogenic hypoxic encephalopathy
11.15 - 11.35	TTM and myocardial infarction David Erlinge, Lund (SE)

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11.15 - 11.35 TTM and myocardial infarction
David Erlinge, Lund (SE)

Session 2:	TTM in cardiac diseases and non-cardiogenic hypoxic encephalopathy
11.55 - 12.15	TTM in acute hypoxic encephalopathy due to non-primary cardiac causes (near drowning, strangulation, etc.) Jonathan Rhodes, Edinburgh (UK)

Targeted temperature management (TTM) is frequently reported in the literature as a therapeutic option in cases of near drowning and strangulation. This probably stems from the fact that many of these cases present late and are in cardiac arrest. It therefore seems logical that management should employ a similar strategy to other causes of cardiac arrest without recovery of consciousness following return of spontaneous circulation. However the majority of the available reports pre date the publication of the TTM trial (1)

Whilst the level of evidence to support (TTM) in this particular subgroup of patients is quite low, none the less, important insights in to the potential value of managing temperature can be gained. Important differences in this population of patients from those arresting due to cardiac causes should also be considered when interpreting results. These issues will be explored.

(1) Nielsen et al 2013. Targeted temperature management at 33°C versus 36°C after cardiac arrest. N Engl J Med.;369(23):2197-206.

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11.55 - 12.15	TTM in acute hypoxic encephalopathy due to non-primary cardiac causes (near drowning, strangulation, etc.) Jonathan Rhodes, Edinburgh (UK)

Session 3: TTM in Neurology and Neurosurgery

13.30 - 13.50 Temperature management and neuroprotection in acute and subacute spinal cord injury
Dalton Dietrich, Miami (US)

Each year thousands of new spinal cord injuries occur that lead to long term deficits and serious quality of life issues. Although a large number of preclinical studies have been conducted to test therapeutic interventions, to date no proven therapeutic modality exist that has demonstrated a positive effect in neurological outcome. This fact emphasizes the need for continuous research in the pathophysiological and treatment of this serious clinical problem. The use of hypothermia has a rich history in terms of treating the detrimental consequences of spinal cord injury. In early clinical studies, local hypothermia was introduced by applying cold fluids to the exposed spinal cord to reduce temperature. Recently, efficient cooling technologies have been developed that allow for mild levels of hypothermia to be induced systemically that appear to show great promise in terms of reducing secondary injury mechanisms and improving functional outcomes. Multiple peer reviewed studies from several laboratories using various models of spinal cord injury have emphasized the beneficial effects of early cooling on targeting secondary injury mechanisms as well as promoting motor and sensory functional improvements. More recently, systemic hypothermia has also been conducted in patients with acute severe cervical spinal cord injuries. Published data from these clinical studies have shown that systemic mild hypothermia induced early after injury and continued over several days followed by a slow rewarming phase has relatively low risk and shows evidence for improved outcomes. Indeed, data from cooled subjects one year after trauma demonstrate an impressive conversion rate from complete to incomplete paralysis. In contrast to hypothermia, mild elevations in temperature (hyperthermia) have been reported to worsen outcome after experimental spinal cord injury. As we continue to advance the use of therapeutic hypothermia and directed temperature management protocols into larger spinal cord injured populations, multi-center randomized trials are now required. Hopefully, future advances will allow these critical studies to be conducted to determine the safety and efficacy of this important therapy.

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Session 3:	TTM in Neurology and Neurosurgery
13.30 - 13.50	Temperature management and neuroprotection in acute and subacute spinal cord injury Dalton Dietrich, Miami (US)

Session 3:	TTM in Neurology and Neurosurgery
14.10 - 14.30	Advances of TTM in spontaneous intracranial haemorrhage Fred Rincon, Philadelphia (US)

Prediction of Basal Metabolic Rate (BMR) in ICH Patients Undergoing Induced Therapeutic Hypothermia Does not Accurately Reflect Resting Energy Expenditure (REE)

Stephanie Dobak, MS, RD; and Fred Rincon, MD, MSc, FCCM, FNCS

Sources of funding: American Heart Association (12CRP12050342) and Academy of Nutrition and Dietetics Research Grant (2014-DNS).

Potential COI. Rincon consultant for Bard Medical.

Introduction.

Prediction of the BMR in stroke patients is performed using conventional validated equations. More objective estimation of nutritional requirements includes measuring the REE by indirect calorimetry (IC). The primary aim of this study was to test the hypothesis that prediction of BMR would over-estimate REE during therapeutic moderate hypothermia (MH, Tcore33-34°C) in ICH patients.

Methods.

During a Phase-IIa/b clinical trial of temperature modulation after ICH, (TTM-ICH, clinicaltrials.gov: NCT01607151), we measured the patient's BMR using the Harris-Benedict (BMR-HB) and modified Penn-State equation (BMR-mPS, which accounts for patient's temperature); and the REE with the Vmax-Encore VS-29n IC System. We performed two measurements of BMR and REE, one at baseline (Day [D] 0) and the second between D1-3. We tested our hypothesis using a single-sided matched pairs t-test for means.

Results.

In total, 7 ICH patients participated in this study, two undergoing MH and three normothermia (NT, Tcore 36-37°C). Median age was 57 years (IQR 22), 55% women, 66% Blacks, median GCS was 7 (IQR 4), median ICH score was 2 (IQR 1), median NIHSS 20 (IQR 5).

For the whole cohort, the mean BMR-HB remained constant from D0 to D1-3 (1315kCal vs. 1283kCal, Delta=-32kCal, p=0.3); the mean BMR-mPS decreased from D0 to D1-3 (1500kCal vs. 1039kCal, Delta=-461kCal, p=0.1); and the REE remained constant from D0 to D1-3 (1184kCal vs. 1217kCal, Delta=33kCal, p=0.5). In the MH group, the BMR-HB was constant from D0 to D1-3 (1330kCal vs. 1250kCal, Delta=-81kCal, p=0.7); the BMR-mPS decreased from D0 to D1-3 (1511kCal vs. 802kCal, Delta=-709kCal, p=0.02); and REE decreased from D0 to D1-3 (1413kCal vs. 1129kCal, Delta= -284kCal, p=0.02).

There were no significant differences in BMRs or REE in the NT group.

Conclusions.

Our data suggests that in ICH patients undergoing therapeutic hypothermia, prediction of BMR may be under-estimated by the BMR-mPS and over-estimated by the BMR-HB. Caloric adjustments during hypothermia may be better assessed by IC.

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14.10 - 14.30 Advances of TTM in spontaneous intracranial haemorrhage
Fred Rincon, Philadelphia (US)

Session 3: TTM in Neurology and Neurosurgery

14.30 - 14.50 Advances of TTM in aneurysmatic subarachnoid haemorrhage
Emanuela Keller, Zürich (CH)

1. Subarachnoid hemorrhage

Major improvements in the management of SAH patients have decreased mortality over the last 30 years by annually 0.9% (Lovelock, Rinkel et al. 2010), but still many survivors continue to have long-term disabilities (Nieuwkamp, Setz et al. 2009). The most important and potentially treatable complication after SAH is the development of intracranial hypertension and delayed cerebral ischemia (DCI), ultimately leading to cerebral infarction or even death. The pathogenesis of DCI is multifactorial and assumed to be initiated in the acute phase after SAH. Early brain injury is triggered by a sudden increase in intracranial pressure and decrease in cerebral perfusion pressure, leading to global ischemia. Mild hypothermia (HT), exerting numerous neuroprotective effects such as decrease in cerebral metabolism(Erecinska, Thoresen et al. 2003), stabilization of the blood-brain barrier, reduction of cerebral edema, suppression of excitatory neurotransmitter concentrations and inflammatory reactions, seems to be well suited as a neuroprotective strategy after SAH. In the following, the application of HT in clinical studies is presented.

2. Hypothermia in patients with poor-grade subarachnoid hemorrhage and/or delayed cerebral ischemia

In a first series of 12 patients with refractory intracranial hypertension or CVS treated with barbiturate coma, Kassell et al. treated 3 patients with moderate HT (30-32°C) (Kassell, Peerless et al. 1980). Yasui et al. investigated changes in cerebral haemodynamic during HT using positron emission tomography in patients with poor-grade SAH (WFNS) 4-5) (Yasui, kawamura et al. 2002). They found a decrease in the cerebral metabolic rate of oxygen (CMRO2) exceeding the decrease in cerebral blood flow (CBF) ipsilateral to the ruptured aneurysm. Seule et al. investigated HT-related side effects and neurological outcome in 100 SAH patients with therapy-refractory intracranial hypertension and/or symptomatic CVS (Seule, Muroi et al. 2009). HT treatment was maintained until ICP normalized, CVS resolved or severe side effects occurred. The mean duration of HT treatment was 7±4 days and the maximum duration was 16 days. Although the majority of patients presented with poor-grade SAH (H&H 4-5 in 66%, Fisher Grade 3-4 in 92%), favourable outcome in 36% of cases. Younger patients (<60 years) more frequently survived with a favourable outcome compared with older patients (39% versus 15%). The most encouraging results were achieved in patients with therapy-refractory CVS without intracranial hypertension, demonstrating favourable outcome in 57% of cases.

Systemic side effects possibly caused from HT and/or barbiturate coma included pneumonia in 52%, thrombocytopenia (<100.000μl) in 47%, septic shock syndrome in 40%, and acute respiratory distress syndrome in 16%. Six patients died of severe side effects (respiratory or multi-organ failure.

3. Conclusions

Given the lack of controlled studies, no general recommendation for therapeutic HT after SAH can currently be made. In poor-grade SAH patients with therapy-refractory intracranial hypertension and/or symptomatic CVS, long-term HT may be helpful in preventing severe disability or death. Given the frequent side effects from long-term hypothermia, besides careful selection of patients, a differentiated standard of neurointensive care with highly specialised treatments is decisive.

Session 3:	TTM in Neurology and Neurosurgery
14.30 - 14.50	Advances of TTM in aneurysmatic subarachnoid haemorrhage Emanuela Keller, Zürich (CH)

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14.30 - 14.50 Advances of TTM in aneurysmatic subarachnoid haemorrhage
Emanuela Keller, Zürich (CH)

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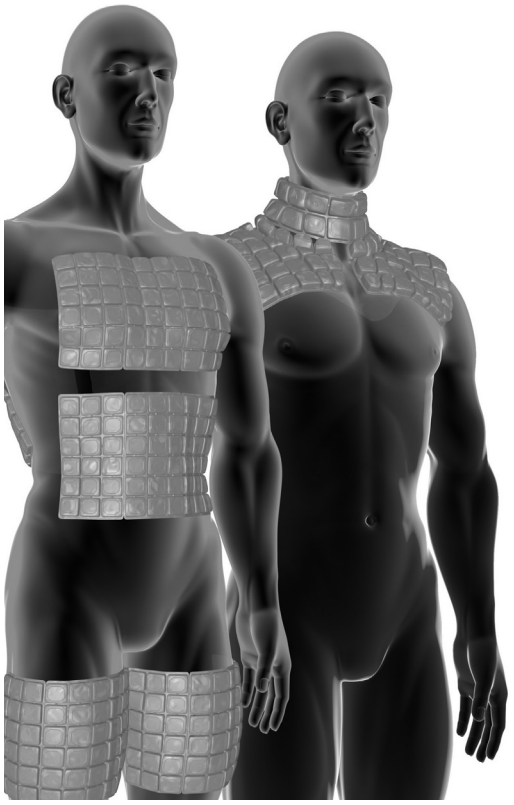

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Session 4:	TTM in Neurocritical Care and Trauma
15.30 - 15.50	TTM in traumatic brain injury Peter Andrews, Edinburgh (UK)

Eurotherm3235Trial

Andrews et al.,

Background:

In patients with traumatic brain injury (TBI) hypothermia can reduce intracranial hypertension; the benefit of hypothermia on functional outcome is unclear.

Methods:

We randomized adults with intracranial pressure (ICP) >20mmHg, despite "Stage 1" treatments (including mechanical ventilation and sedation management), to standard care (control group) or hypothermia 32-35°C plus standard care. In control group, "Stage 2" treatments (e.g. osmotherapy) were added as needed to control ICP. In hypothermia group, "Stage 2" treatments were added only if hypothermia failed to control ICP. In both groups, "Stage 3" treatments (barbiturates, decompressive craniectomy) were used if all "Stage 2" treatments failed to control ICP. Primary outcome was the Extended Glasgow Outcome Scale (GOSE, range 1 (dead) to 8 (upper good recovery)) at 6 months. The treatment effect was estimated with ordinal logistic regression as a common odds ratio (OR), adjusted for pre-specified prognostic factors (OR<1.0 favors hypothermia).

Results:

We enrolled 387 patients at 47 centers in 18 countries from 2009 to 2014 when recruitment was suspended following safety concerns. "Stage 3" treatments were required to control ICP in 54% in control group and 44% in hypothermia group. The adjusted common OR for GOSE was 1.53 (95% confidence interval, 1.02 to 2.30, p=.04, indicating worse outcome in hypothermia group). Favorable outcome (GOSE 5-8, moderate disability-good recovery) was achieved by 26% in hypothermia and 37% in control group (p=0.03).

Conclusions:

In patients with ICP >20mmHg after TBI, therapeutic hypothermia plus standard care to reduce ICP did not improve outcomes compared with standard care alone. (Current Controlled Trials number, ISRC-TN34555414)

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15.30 - 15.50 TTM in traumatic brain injury
Peter Andrews, Edinburgh (UK)

Session 4: TTM in Neurocritical Care and Trauma

15.50 - 16.10 TTM and ICP/CPP
Julian Bösel, Heidelberg (DE)

Miscellaneous brain pathologies can develop a space-occupying effect and lead to a critical increase in intracranial pressure (ICP) with threatening cerebral herniation and / or critical decline in cerebral perfusion pressure (CPP). Quite often, this occurs as a consequence of edematous secondary brain injury from severe traumatic brain injury (TBI), subarachnoid hemorrhage (SAH), severe ischemic (AIS) or hemorrhagic stroke (ICH) as well as neoplastic, infectious or inflammatory diseases. In addition or alternative to other measures to reduce ICP (such as deep sedation, osmotherapy, decompressive surgery, etc.), targeted temperature management (TTM) has been recognized as an effective tool to control ICP. Not only has induced hypothermia proven effective as part of an escalative ICP-protocol in severe TBI (1) and is currently guided according to its effect on ICP in the large EUROTHERM TBI trial (2). Also, induced normothermia was shown associated with less ICP crises in TBI patients (3) and less metabolic stress during ICP crises in SAH patients (4). In the presentation, these and more examples for the utility of TTM for controlling ICP and stabilizing CPP will be addressed, with the focus not so much on the specific underlying primary pathologies but more on the ICP-reducing principle of TTM in secondary brain injury (mainly edema), the way and timing of TTM application, and its integration in comprehensive ICP/CPP-management protocols. As far as available studies allow and mainly indirectly, hypothermia and normothermia will be compared with regard to their ICP-controlling capacity.

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2. *Andrews et al., Trials 2011*
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15.50 - 16.10 TTM and ICP/CPP
Julian Bösel, Heidelberg (DE)

November 20, 2015

Session 4:	TTM in Neurocritical Care and Trauma
16.10 - 16.30	TTM and advanced neuromonitoring Raimund Helbok, Innsbruck (AT)

The impact of therapeutic hypothermia (TH) on long-term neurological outcome is still controversial. Data on the effects of TH on brain homeostasis are mostly derived from experimental research. Invasive multimodal neuromonitoring techniques provide additional insight into pathophysiological changes in humans associated with primary or secondary brain injury. Large evidence exists that fever is associated with worse neurological outcome after acute brain injury. Decreasing elevated body temperature to normothermia reduces cerebral metabolism and should be a target in all patients with acute brain injury. Hypothermia may further beneficially influence brain homeostasis, however the temperature goal and duration is still controversial. Moreover, induction of hypothermia and in specific the rewarming period may abolish the benefit of therapeutic hypothermia. Therefore adequate monitoring and an individual approach may be necessary. Here we present an updated review about existing data on brain physiologic and pathologic changes during temperature modulation in patients with acute brain injury.

We call for more research using multimodal neuromonitoring techniques in patients undergoing TH to optimize cooling and rewarming strategies.

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16.10 - 16.30 TTM and advanced neuromonitoring
Raimund Helbok, Innsbruck (AT)

Session 4: TTM in Neurocritical Care and Trauma

16.30 - 16.50 TTM in polytrauma
Peter Paal, Innsbruck (AT) / London (UK)

Accidental hypothermia (i.e. core temperature <35°C) in multiple trauma is an independent risk factor for increased mortality. Multiple trauma patients are prone to accidental hypothermia because central and peripheral thermoregulation are inhi-bited due to haemorrhage (underperfusion of thermoregulation centres in the brainstem), reduced or abolished shivering, and vasodilation due to analgosedation (possibly less pronounced with ketamine).

Accidental hypothermia is more frequent in winter but must be expected at all seasons of the year, even in regions with a warm climate.1 The incidence of mutliple trauma patients admitted with accidental hypothermia is underestimated, but may exceed 30%.1 The low awareness of accidental hypothermia is in part owed to ther-mometers, which are unreliable in cold environments, and insufficient insulation and rewarming measures out of hospital.

A metaanalysis in elective surgery patients reported that even mild hy-pothermia (i.e. temperature reduction by 1°C) increased bleeding (+16%) and increa-sed also transfusion requirements (+22%).2 Other studies reported similar results.3 In multiple trauma patients hypothermia is part of the deadly triad, consisting of (respiratory and metabolic) acidosis, haemorrhage, and hypothermia; and may if not sufficiently counteracted, result in death. A decrease in core temperature does exponentially increase mortality. Positive correlations between hypothermia and increased mortality have been reported in patients with burns,4 hip fractures,5 ruptured abdominal aortic aneurysm,6 and multiple trauma.7 Studies found a positive correlation between degree of accidental hypothermia, and surgical site infection,8 multi-organ failure,9 and mortality.10

Routinely, coagulation monitoring is performed at 37°C. Thus, coagulopathies related to hypothermia will not detected. Thus, in hypothermic patients, coagulation analyses should be temperature corrected to the core temperature of the hypothermic patient. Out of hospital, better insulation and rewarming is warranted. Implementation of the available knowledge and equipment is required.11,12 Rewarming should be started as soon, and as aggressively, as possible. In multiple trauma patients with spontaneous circulation in hospital rewarming should be performed aggressively with external warm forced air and minimially invasive with warm infusions, and operating theatres adequately warmed to counteract heat loss of extensively uncoverd body parts during surgery.13 In patients with primarily hypothermic cardiac arrest and multiple trauma rewarming with extra corporeal membrane oxygenation should be considered.14 15

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16.30 - 16.50 TTM in polytrauma
Peter Paal, Innsbruck (AT) / London (UK)

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16.30 - 16.50 TTM in polytrauma
Peter Paal, Innsbruck (AT)

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Session 5:	TTM and Infection/Inflammation
08.30 - 08.50	TTM and sepsis/septic shock Jonathan Rhodes, Edinburgh (UK)

The control of high body temperatures in patients with sepsis has strong historical associations and intuitively seems the correct thing to do. Indeed this view is often reinforced those with commercial interests. Furthermore several sound reasons for controlling temperature are often cited in the literature, reinforcing the perception that the control of fever in the septic patient is appropriate, reducing suffering and improving outcome.

However, the development of a fever in response to infection is common in many animals. It is the consequence of the resetting of the hypothalamic thermoregulatory set point to a higher value. Vasoconstriction, increased muscle tone and shivering then follow, conserving/generating heat. It could be argued that such a stereotyped response is the product of evolution and therefore should confirm a survival advantage to the host. Indeed evidence that increased body temperature prejudices infectious organisms or increases the efficacy of antibiotics exists in the literature. Furthermore observational studies have reported that fever is associated with survival in particular critical care populations.

This talk will review the evidence for and against the control of body temperature in patients with sepsis. In particular clinical trials of antipyretic treatment strategies will be examined.

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08.30 - 08.50 TTM and sepsis/septic shock
Jonathan Rhodes, Edinburgh (UK)

Session 5: TTM and Infection/Inflammation

08.50 - 09.10 TTM and acute bacterial meningitis and viral encephalitis
Erich Schmutzhard, Innsbruck (AT)

Fever is very frequently seen in neurocritical care patients, and even in febrile intensive care patients, without neurological injury, fever is frequent. Most intensivists prefer to intervene to lower body temperature below 39.0 ° C, with first-line preference being a combination of paracetamol and physical cooling, second-line interventions include intensive physical cooling.

Fever is a frequent hallmark in viral encephalitis and severe bacterial meningitis, both diseases requiring neurocritical care management. Brain edema may be seen in acute viral encephalitis and acute bacterial meningitis, hydrocephalus, pyocephalus, vasculitis/arteritis leading to brain infarctions, septic sinus or venous thrombosis, cerebritis and brain abscess formation are complications in acute bacterial meningitis frequently adding to neuronal injury. In acute bacterial meningitis, invasive ICP management has been shown to reduce mortality (Glimaker et al, 2014). Similarly, patients with severe acute viral encephalitis leading to increased intracranial pressure and thereby adding to neuronal injury has been shown to benefit from invasive methods as therapeutic hypothermia and/or decompressive craniectomy.

Recently, a randomized clinical trial of induced hypothermia in severe bacterial meningitis has been published with highly conflicting results (Mourvillier et al, 2013). Neither intracranial pressure nor cerebral perfusion pressure monitoring was part of the trial protocol, the overall mortality in this cohort of patients was very high (37 %.. Up to 3000 mL of iced saline were infused to achieve the target temperature, but no information had been given on hemodynamic parameters. The passive rewarming from 33° to 37° was done in a median of 14 hours (i.e. 0.4°C per hour!) in the most vulnerable phase of severe acute bacterial meningitis. It is known that both, brain edema and secondary ischemic lesions (both, arterial and venous) occur within this critical phase of disease. In patients suffering from severe inflammation and severe inflammatory response syndrome, antipyretics and antiphlogistics may influence the course and these drugs were withheld in the hypothermia group.

The fact that a median of 1 patient was recruited per center over the entire recruitment time of almost 3 years gives rise to discussion, as does the fact that a median time of 2.6 hours elapsed between arrival into the hospital and i.v. administration of antibiotics. In addition, the question is to be answered why 5.8 h elapsed until the first dexamethasone dose was given (in the hyperthermia group) and 4.3 h in the control group. In infectious disease neurology it is absolutely accepted common sense that the first dexamethasone dose should be given immediately prior to the first antibiotic chemotherapeutic dose.

Every patient with acute severe bacterial meningitis or severe viral encephalitis suffering from signs and symptoms of highly increased intracranial pressure needs to have an external ventricular drain or an ICP probe. Increased ICP and decreased CPP respectively need to be treated in a neuro-ICU as aggressively as possible, avoiding secondary brain damage. Such aggressive management of increased ICP/decreased CPP also eventually must include targeted temperature management. The target needs to be the ICP and the CPP respectively.

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08.50 - 09.10 TTM and acute bacterial meningitis and viral encephalitis
Erich Schmutzhard, Innsbruck (AT)

Session 5: TTM and Infection/Inflammation

09.30 - 09.50 TTM and severe infection: from targeted temperature management to permissive hyperthermia
Erich Schmutzhard, Innsbruck (AT)

In experimental sepsis accompanying mild hypothermia and artificial mild hypothermia both reduce mortality, alleviate systemic inflammatory responses and the damages to various organs Induced mild hypothermia delays the evolution of cytokines and metabolic acidosis in experimental sepsis

There is considerable variability in attitudes to fever management with reported tendency to actively reduce fever in febrile patients with sepsis, in particular in febrile intensive care patients without neurological injury (Saxena et al, 2011). Recently, the presence of spontaneous hypothermia (< 36°C) within 24 hours of sepsis was shown to be a significant independent predictor of sepsis-induced immunosuppression and sepsis-associated mortality (Drewry et al, 2015). This led to the assumption that "cold sepsis" might carry a risk of increased mortality, most likely as a result of "frozen immune response". It is true that up to 20 % of patients with sepsis present spontaneously with hypothermia and experience a mortality rate roughly twice that of their pyrexic peers. However, this holds true for spontaneous hypothermia, i.e. spontaneous temperature variability. Better temperature monitoring and temperature control measures might – even at the level of cold sepsis, i.e. < 36°C – potentially exert a less "freezing" impact onto the immune response in these septic patients.

On a cellular level, normal body temperature (37°C) has been shown not to restore normal monocyte function in vitro, whereas temperature levels of 39°C partially were capable to reverse the effect of hypothermia onto monocyte function. These data confirm that warming up to normal body temperature (37°C) does not restore fully normal monocyte function in vitro; therefore, these data might be interpreted – if extrapolated to patients' care - that hypothermic patients should be warmed up even higher, i.e. into febrile temperature ranges. Whether this holds true also in vivo, i.e. in patients, needs to be studied carefully, in particular in patients suffering from additional neuronal lesions. However, what truly can be extrapolated from these data is the comprehension why hypothermia leads to an increase of infectious complications in patients undergoing therapeutic hypothermia / targeted temperature management (Billeter et al, 2015).

Severe sepsis and/or septic shock is associated with multi-organ failure including the coagulation system; therefore it has been hypothesized that mild induced hypothermia might even add to coagulopathy. Very recently Johanssen et al (2015) showed, when analyzing data from an ongoing randomized controlled trial, the Cooling And Surviving Septic shock study (CASS), that functional coagulopathy (caused by sepsis/septic shock) improved during the hypothermia phase when measuring reaction time and maximum amplitude in thrombelastography in septic patients, compared to controls. This improvement of functional coagulopathy parameters during the hypothermia intervention persisted even after rewarming. Whether this positive effect on sepsis-related coagulopathy can be transformed to improved survival still needs to be determined.

Whereas these data suggest that cautious targeted temperature management might even improve outcome in severe sepsis patients, Kushimoto et al showed in the JAAM Sepsis Registry Study Group that patients with body temperature spontaneously being < 36.5°C had significantly worse sequential organ failure assessment scores (SOFA scores) when compared with patients with body temperature > 37.5°C on the day of enrolment. Also the 28 day and hospital mortality was significantly higher in the first group of patients (< 36.5°C). Whether this higher mortality rate is directly the consequence of the spontaneous hypothermia or whether this hypothermia simply indicates a more severe and more advanced state of the disease, still needs to be studied and cannot be extrapolated from the data in this sepsis registry (Kushimoto, 2013; Young, 2014). In addition, body temperature was not maintained on a safe and static/stable level, therefore in both groups, in particular those with initial unintentional hypothermia, temperature variability might have played a decisive role in influencing the prognosis.

Septic patients frequently show multiorgan failure attributable to endotoxemia. Schwarzl et al (2013) showed that the induction of mild hypothermia attenuates cardiac and respiratory dysfuntion and counteracts sympathetic activation during experimental endotoxemia, indicating a reduction of cytokine responsiveness induced by mild hypothermia.

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Session 5:	TTM and Infection/Inflammation
09.30 - 09.50	TTM and severe infection: from targeted temperature management to permissive hyperthermia Erich Schmutzhard, Innsbruck (AT)

Recently, Costa-Lara and Varon discussed the highly interesting question - in an editorial of the Am J Emerg Med - whether therapeutic hypothermia should be used in sepsis or not and eventually came up with the statement, corroborated by the findings on the role of autonomic nervous system function on hypothermia-mediated sepsis protection, that therapeutic hypothermia confers a beneficial effects in experimental sepsis. Not only biomarkers were changed to the better, but also mortality was significantly reduced in those rats suffering from severe sepsis that had undergone hypothermia. They conclude that sepsis should never be a contraindication to institute therapeutic hypothermia in critically ill patients if they need this therapeutic strategy.

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09.30 - 09.50 TTM and severe infection: from targeted temperature management to permissive hyperthermia
Erich Schmutzhard, Innsbruck (AT)

Session 6:	TTM and and then - Rewarmingh: when how and how long, Post-hypothermia temperature management
10.30 - 10.50	Prognostication in patients with TTM, including withdrawal of care in TTM-patients Christoph Leithner, Berlin (DE)

After cardiac arrest (CA) and resuscitation, the majority of patients remains comatose and is treated on an intensive care units. Around half of those who survive suffer from severe hypoxic encephalopathy (HE) leading to unresponsive wakefulness syndrome or death. To limit suffering of next-of-kins and futile intensive care, withdrawal of treatment is frequently performed in patients without a chance to recover relevant cognitive abilities. Because withdrawal of treatment rapidly leads to the death of these critically ill patients, prognostication of poor outcome needs to be done with a positive predictive value close to 100%.

A large number of studies have investigated parameters for early outcome prediction. These include repeated neurological examination, biomarkers such as neuron specific enolase (NSE), electrophysiological testing (somatosensory evoked potentials (SSEP) and electroencephalography (EEG)) and brain imaging (computed tomography (CT) or magnetic resonance tomography (MRI)). Most are tested 72 hours after cardiac arrest. Thus, testing is generally performed after normothermia has been reached in patients who received targeted temperature management (TTM).

Recent studies show that absence of a motor reaction to painful stimuli is not a reliable predictor of poor outcome. Bilaterally absent pupillary light reaction is more specific. A large substudy from the TTM trial indicated a cut-off for NSE of 50 ng/ml, above which good outcome was not observed. Other studies have found higher thresholds and confounders such as hemolysis, NSE producing tumors and acute brain diseases other than HE need to be considered. Bilaterally absent median nerve SSEP are highly predictive of poor outcome after cardiac arrest. Only few patients with good outcome despite this finding have been reported. Care must be taken to ensure a high recording quality and interrater reliability is not perfect. A recent study suggests that high amplitude SSEP may predict absence of severe HE incompatible with regaining consciousness. Early EEG is important to detect status epilepticus which may occur without visible myoclonus. A subset of patients may recover with good outcome despite Status epilepticus if aggressively treated.

Several EEG pattern are predictive of poor outcome, but sedation needs to be taken into account as important confounder. Finally, brain imaging is an important tool for outcome prediction. Early brain imaging (upon arrival in the emergency room) should be performed in patients with possible intracranial etiology of cardiac arrest, such as subarachnoid hemorrhage (frequent in Asian populations). Quantification of brain density changes in HE can be obtained as 'gray-white-matter-ratio' (GWR) and my help to reduce interrater-variability of brain CT interpretation. Thresholds for poor outcome are debated and the optimal timing of brain CT for outcome prediction is unclear, although recent evidence suggests that waiting for at least 24 hours may increase sensitivity. Brain MRI can depict the spatial heterogeneity of HE and quantification of the apparent diffusion coefficient may be used to predict outcome.

For clinical routine, most authors recommend repeated neurological examination, a significant waiting period of several days and a multiparameter approach to ensure high reliability of poor outcome prognostication.

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10.30 - 10.50	Prognostication in patients with TTM, including withdrawal of care in TTM-patients Christoph Leithner, Berlin (DE)

Session 6:	TTM and and then - Rewarmingh: when how and how long, Post-hypothermia temperature management
10.50 - 11.10	Rewarming, how and how fast - evidence for individualised rewarming Markus Foedisch, Bonn (DE)

Temperature management in different levels of target temperature today is standard care in the bundle of therapeutic approaches in comatose survivors of cardiac arrest. It is the only therapy applied that has shown to be effective in increasing survival and improvement of neurological outcome. Targeted temperature management after cardiac arrest consists of three phases, induction, maintenance and rewarming; the majority of studies in recent years have been targeting issues like target temperature, duration and speed of cooling. There are only few clinical data available showing effects of rewarming strategies after therapeutic hypothermia on postischemic brain injury and inflammatory response of different organs after cardiac arrest, brain injury and septicemia. Most available data concerning the speed of rewarming derived from animal models of brain injury, in patients undergoing aortic surgery and investigations of therapeutic hypothermia in patients after brain injury. These mechanism can also be seen as responsible for further or secondary neurological damage in post-cardiac arrest patients showing different stages of global cerebral ischemia. All those studies show that fast rewarming after therapeutic hypothermia impairs brain circulation and potentially worsen the neurological outcome of the individuals. It could be shown that rapid rewarming to normothermia within 10 min not only reverses the neuroprotective effects of hypothermia but could double the axonal damage. A similar effect could be demonstrated on cerebral microcirculation. The hypothermia induced protection against impairment of microcirculation can be completely reversed or the injury increased under the influence of high-speed rewarming.Therefore a rewarming rate between 0,25°C and 0,5°C after targeted temperature management found input into treatment strategies and recommendations for post-resuscitation care. The question after the optimum rewarming rate still remains unanswered, it is also unknown whether the initial severity of the brain damage or other cooling strategies and durations have potential influence on the rewarming rate. Further studies are needed not only to evaluate the importance of duration of targeted temperature management but also the impact of the speed of rewarming on organ function and neurological outcome.

According to all recent publications a high speed rewarming counteracts every benefit given by temperature management and mild therapeutic hypothermia and slowing down the rate of rewarming seems to be essential to avoid the negative rebound effects assuring maximal efficacy following the use of hypothermic intervention.

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10.50 - 11.10 Rewarming, how and how fast - evidence for individualised rewarming
Markus Foedisch, Bonn (DE)

Session 6:	TTM and and then - Rewarmingh: when how and how long, Post-hypothermia temperature management
11.10 - 11.30	Post-hypothermia temperature management Gregor Brössner, Innsbruck (AT)

Fever (i.e. body core temperature >38°C) is an independent predictor of poor neurological outcome in patients with severe acute neuronal injury (Greer, Funk, Reaven, Ouzounelli, & Uman, 2008). Therapeutic targeted hypothermia (TH) is used in various conditions in intensive care medicine for its neuro-protective purpose (Choi, Badjatia, & Mayer, 2012). Robust data on the beneficial effect on outcome of TH exist among others for post resuscitation care, post-anoxic encephalopathy of neonates, resistant elevation of intracranial pressure and hepatic encephalopathy (Choi et al., 2012; Hypothermia after Cardiac Arrest Study Group, 2002; MD et al., 2015; Nielsen et al., 2013). Many protocols of TH include a cooling phase of 24 or even more hours followed by a rewarming phase that should ideally be done controlled and rather slowly (i.e. 0.1 – 0.25°C per hour). However, the role of targeted temperature management after the rewarming phase is completed, the patient being at normothermia (36.5-37°C), is discussed controversially (Vanhengel, De Deyne, & Dens, 2013). Given the fact the neurological remodelling processes after acute brain injury are thought to last days and even weeks some authors suggest not only measuring temperature but also controlling it actively over a long-term period.

The rate of rebound hyperthermia or simply fever (i.e. body core temperature >38°C) after TH in post resuscitation is well documented and published to be around 40% (Bro-Jeppesen et al., 2013; Cocchi et al., 2014). If this rebound temperature elevation has an effect on outcome is discussed controversially although the only prospective trial investigating this question so far shows significant worse outcome of patients being febrile post TH (Bro-Jeppesen et al., 2013).

We conducted a prospective-randomized trial with endovascular based normothermia with a targeted temperature of 36.5°C over 168 or 336 hours in patients with severe cerebrovascular disease (Broessner et al., 2009). In this trial we observed a temperature elevation in the post endovascular temperature management phase in some patients although none of the respective patients were at hypothermia level. Taken together we think that in patients with acute severe neuronal injury, body (or even brain-) temperature has to be monitored continuously, but also controlled actively to strictly avoid fever over a long-term period.

Therefore future study should also focus on the post TH phase and include a temperature protocol addressing the question of prolonged controlled normothermia after TH.

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11.10 - 11.30 Post-hypothermia temperature management
Gregor Brössner, Innsbruck (AT)

Session 7: What makes TTM sometimes so difficult

13.00 - 13.20 TTM - pharmacokinetics and pharmacodynamics
Christian Storm, Berlin (DE)

Introduction

Current international guidelines recommend a target temperature management (TTM) in post cardiac arrest patients. Early neurological assessment and prognostication turned out to be difficult in patients after or during a TTM. Therefore, guidelines recommend the use and combination of several different methods for prognostication [1]. Post cardiac arrest patients undergoing a TTM need deep sedation to tolerate cooling and to avoid side effects such as shivering. Lowering the body temperature and deep sedation after cardiac arrest with more or less severe hypoxia might increase the difficulty in reliable prognostication but only few data are published regarding this important question.

Pharmacokinetics and dynamics in TTM

Different drugs are used for sedation in post cardiac arrest patients. The idea of using short-acting drugs with a short half-life-time such as Propofol, for example, seems a good solution to avoid any accumulation and influence on prognostication. However it has been shown that Propofol significantly decreases hepatic blood flow in combination with mild hypothermia (34° vs. 37°C) in an intraoperative setting with healthy volunteers leading to higher blood concentrations in mild hypothermia [2]. Current guidelines in Germany recommend volatile sedation in ICU as equal to intravenous sedation if fast wake up time and good recovery of cognitive function is requested [3]. Volatile sedation is feasible in ICU with an anesthesia conserving device (ACD) for vaporization of different gases. As long time volatile sedation is still off-label use, only a few different substances have been evaluated so far. With short half-lifetime and no accumulation volatile sedation is very well controllable in general [4]. Isoflurane is widely used in different patient subgroups and obviously has the best risk-benefit profile without being influenced by hypothermia itself regarding pharmacokinetics and dynamics (unpublished data; Storm et al).

Liver function and drug metabolism such as activation of prodrugs or clearance of drugs might also be influenced by different target temperatures during TTM after cardiac arrest. Clopidogel is a prodrug that needs to be activated by liver enzyme CYP3A4 subtype to be a potent platelet inhibitor. Although novel drugs for platelet inhibition are available Clopidogrel is still widely used in patients. Firstly, intestinal absorption might be reduced during cooling and second, liver enzyme activity might also be reduced [5]. Due to this, the activation of prodrugs, which is dependent on liver enzymes, seems possibly affected.

To determine liver function before or after transplantation, the novel LiMAx-test (maximum liver function capacity) has been developed as point-of-care test [6]. LiMAx is a dynamic test based on C-methacetin kinetic reflecting CYP1A2 activity. Although in the majority of post cardiac arrest patients undergoing TTM transaminases and liver coagulation parameters are within the normal range, the CYP1A2 activity is significantly reduced with a temporary correlation to TTM itself (unpublished data; Storm et al.).

Conclusion

In conclusion, target temperature management can and will influence drug pharmacokinetics and dynamics in several ways. This needs to be taken into account in terms of reliable prognostication and regarding the use of many drugs, especially for important platelet inhibitors and sedation.

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Session 7:	What makes TTM sometimes so difficult
13.00 - 13.20	TTM - pharmacokinetics and pharmacodynamics Christian Storm, Berlin (DE)

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Notes

13.00 - 13.20 TTM - pharmacokinetics and pharmacodynamics
Christian Storm, Berlin (DE)

Session 7: What makes TTM sometimes so difficult

13.40 - 13.50 TTM - and muscle relaxants
Mathias Stöckl, Vienna (AT)

THE NECESSITY OF SKELETAL MUSCLE PARALYSIS IN PATIENTS DURING MILD THERAPEUTIC HYPOTHERMIA AFTER CARDIAC ARREST.

RESULTS OF A PROSPECTIVE RANDOMIZED, DOUBLE BLINDED, DOUBLE DUMMY STUDY.

M. Stöckl 1, F. Sterz 1, M. Holzer 1, C. Weiser 1, A. Schober 1, C. Testori 1, J. Kechvar-Parast 2, G. Nichol 3, M. Frossard 1, H. Herkner 1, A. Laggner 1, H. Losert 1.

1 Department of Emergency Medicine, Medical University of Vienna, Vienna, Austria.

2 Department of Neurology, Medical University of Vienna, Vienna, Austria.

3 Department of Medicine, University of Washington, Seattle, Washington.

Introduction:

Current guidelines recommend therapeutic hypothermia (TH) to improve neurological outcome after cardiac arrest (CA).[1,2] Besides analgesia and sedation, neuromuscular blockers (NMBs) are often used during induction and maintenance of TH in order to prevent shivering [3], which leads to temperature counter-regulation, increases metabolic demands and thereby counteracts the beneficial effects of mild TH. However, NMBs are reported to be associated with side effects and prolonged intensive care stay. Importantly, their use may mask epileptic activity, thus post hypoxic seizures might remain undetected. [4,5]. The American Heart Association Guidelines 2010 specify that „the duration of neuromuscular blocker agents should be kept to a minimum or avoided altogether".[1]. Therefore we compared a continuous administration of NMB to a demand-oriented strategy.

Methods:

This prospective randomized double blind, double dummy trial allocated 63 patients receiving TH after resuscitation from CA.

The primary outcome was the number of shivering episodes during TH. Further outcomes included survival and neurological status one year after CA, time to awakening, length of stay at hospital and ICU as well as required cumulative dose of rocuronium, midazolam and fentanyl, time to target temperature and cooling rate. The study was approved by a research ethics committee.

Results:

Sixty-three patients (32 continuous NMB group; 31 bolus NMB group) were enrolled from November 2010 to September 2013.

Mean age was 60±12 years and 83% had male gender. Differences in baseline characteristics at hospital admission were not significant.

Shivering episodes were detected in 94% in the bolus group compared to 25% in patients receiving continuous rocuronium infusion. Patients randomized to the continuous NMB group received significant lower doses of midazolam (4.3±0.8mg/kg vs. 5.1±0.9mg/kg, p=0.000) and fentanyl (0.062±0.014mg/kg vs. 0.071±0.007mg/kg, p=0.000), but required higher cumulative doses of rocuronium (7.8±1.8mg/kg vs. 2.3±1.6mg/kg, p=0.000). Still earlier awakening (2 [IQR 2;3] days vs. 4 [IQR 2;7.5] days, p=0.038) and decreased length of stay at the ICU (6 [IQR 3;5.9] days vs. 10 [IQR 5;15] days, p=0.029) were observed in the continuous NMB group. There were no differences in survival and quality of life after 12 months of observation. Differences in the number of days awake until 28 days after CA were not significant.

Session 7: What makes TTM sometimes so difficult

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Mathias Stöckl, Vienna (AT)

Continuous administration of NMBs did not influence the cooling rate (mean 0.05±0.02°C/kg/hour in patients allocated to the continuous NMB group vs. 0.06±0.03°C/kg/hour) or lactate clearance and distinction in time to target temperature (mean 45 [IQR 23;58] minutes in the continuous NMB group vs. 31 [IQR 31;75] minutes in the bolus NMB group) turned out to be non-significant.

Conclusion:

Randomization of patients resuscitated from CA to continuous NMB or bolus NMB was feasible.

Continuous muscle paralysis with rocuronium during the first day after resuscitation reduced shivering, midazolam and fentanyl requirement as well as time to awakening and discharge from ICU. There were no differences in overall survival as well as cooling rate and time to target temperature.

ClinicalTrials.gov Identifier: CT01719770

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13.40 - 13.50 TTM - and muscle relaxants
Mathias Stöckl, Vienna (AT)

Session 8: TTM - From Current Practice to Future Perspectives

14.30 - 14.50 Cooling - rewarming - maintenance of normothermia
Gregor Brössner, Innsbruck (AT)

The first studies investigating the neuro-protective properties of induced hypothermia were done back in the early 50ies. With the development of novel cooling devices in the late 90ies targeted temperature management was again investigated in randomized trials in various acute neurological diseases including post resuscitation care, stroke, traumatic brain injury, post-anoxic encephalopathy of neonates, resistant elevation of intracranial pressure and hepatic encephalopathy (Broessner et al., 2009; Crossley et al., 2014; Hypothermia after Cardiac Arrest Study Group, 2002; MD et al., 2015; Nielsen et al., 2013). Studies in resuscitated patients in the early 2000 delivered very promising results but follow up trials question the actual depth of TTM.

Today there is overwhelming data that avoidance of fever or even therapeutic hypothermia is beneficial in various animal models of acute brain injury (Choi, Badjatia, & Mayer, 2012; van der Worp, Sena, Donnan, Howells, & Macleod, 2007). However, solid evidence of TTM increasing good (neurological-) outcome in humans is still limited. As a consequence there are no consistent recommendations for TTM but rather different protocols in terms of inclusion criteria (i.e. patient selection), length of cooling, speed of rewarming, selection of cooling devices, post hypothermia temperature control and treatment of side effects such as shivering (Fischer et al., 2015; Hoedemaekers, Ezzahti, Gerritsen, & van der Hoeven, 2007; Nielsen et al., 2013; Polderman & Varon, 2015). The critical care community is currently challenged by different approaches towards up-to-date TTM.

Questions that should urgently be investigated in future trials in order to create standardized protocols for clinical use:

- Are there any biomarkers that allow patient selection for TTM and maybe guide clinicians through length and depth of cooling?
- Pharmacokinetic and pharmacodynamic changes of drug metabolism and nutrition under TTM?
- Optimal treatment of complications that accompany TTM, especially shivering?
- What are the pathophysiological details that drive the neuro-protective effect of TTM?

A pilot trial investigating controlled normothermia in cerebrovascular disease patients revealed the cool bath temperature of the feedback device was associated with outcome {Fischer:2015bk}. This may be a first hint how to select patients or guide TTM therapy.

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Session 8: TTM - From Current Practice to Future Perspectives

14.30 - 14.50 Cooling - rewarming - maintenance of normothermia
Gregor Brössner, Innsbruck (AT)

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14.30 - 14.50 Cooling - rewarming - maintenance of normothermia
Gregor Brössner, Innsbruck (AT)

Session 8: TTM - From Current Practice to Future Perspectives

14.50 - 15.10 Future aspects of TTM: cooling by drugs?
Rob Henning, Groningen (NL)

Nature has basically solved the problems associated with hypothermia and rewarming: hibernation. During hibernation, on the northern hemisphere usually lasting from October to May, animals enter torpor, periods of about 1-2 weeks during which body temperature drops to ambient temperatures, ranging typically between 2-8 0C. Torpor periods are alternated with so-called interbout arousals, brief periods (<24 h) during which animals fully rewarm [1]. The gross additional physiological changes during torpidity, including e.g. a drop in heart and respiratory rate by >90%, are also fully reversed shortly after arousal. Moreover, the transition from torpor to arousal is extremely fast: e.g. Golden hamster fully rewarms from 7 0C to 37 0C in about 90 min [2]. Remarkably, hibernators endure this repetitive cooling and rewarming cycles without any organ damage.

In the past years, we have explored mechanisms employed by hibernators to attenuate hibernation associated organ damage in Golden hamster. In addition to a suppression of its immune system [2-4], hibernators also deploy protective mechanisms, allowing them to cope with excess oxidative stress. We found increased H2S production, through serotonin stimulation of cystathionine-beta-synthase (CBS), to constitute an important mechanism in hamster cells, which is also operational in cells of non-hibernators [5, 6].

Based on this finding, we initiated the development of a range of compounds that allow safe, deep cooling of cells of various origins. In my presentation, I will briefly introduce hibernation and discuss protective strategies hibernators' employ. Further, I will discuss data on these compounds' mechanism of action and share data on their efficaciousness in preserving organ function following deep cooling and rewarming of the in vivo rat.

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Session 8: TTM - From Current Practice to Future Perspectives

15.10 - 15.30 Future aspects of TTM: new cooling devices?
Kees Polderman, Pittsburgh (US)

Therapeutic temperature management (TTM), encompassing fever control and therapeutic hypothermia (TH), has become an increasingly important therapeutic target in critically ill patients with any type of acute brain injury, and is being studied in acute myocardial infarction (MI) and ischemic stroke. A "heated" debate is currently ongoing regarding the optimal temperature that should be applied to treat patients with post-anoxic brain injury following cardiac arrest (CA); however, there is general consensus on the importance of temperature management in these patients [1-2]. For some indications (e.g. mitigating myocardial injury in acute MI), the speed of cooling appears to a crucial factor in determining efficacy; for other indications, accuracy and precision of temperature maintenance may be more important [3-4]. Slow and controlled re-warming is a key element of effective TTM in all patient categories, as benefits of TTM can be completely negated by rapid re-warming and by episodes of fever occurring after TH treatment [3-5].

Data from two large retrospective studies and, recently, from a prospective multicenter RCT comparing endovascular to basic surface cooling in CA patients demonstrate that the new generation of cooling devices (specifically endovascular cooling) can control temperature safely and effectively, and suggest that more effective and stable temperature control may lead to improved neurological outcomes [4,6-8]. A new batch of cooling devices and novel cooling technologies that can enable us to better control temperature, and enhance cooling speeds, have been developed and are at various stages of development; some have been/are being tested in clinical trials, some have recently been FDA and/or EMEA approved. These include devices such as automated peritoneal lavage (APLS), esophageal cooling, next generation endovascular cooling catheters, and others. APLS enables very rapid TH induction, with cooling speeds of up to 14oC/hour [9]; the Proteus endovascular catheter may enable cooling speeds of 10oC/hour (personal communication). Esophageal cooling is much less fast, but potentially combines some benefits of invasive cooling with the ease of non-invasive cooling.

Basic measures such as cold fluid infusion still have an important place in TTM. However, a recently published large multicenter RCT suggests that administration of large volumes of refrigerated fluids in the field could lead to higher rates of re-arrest and pulmonary edema [10]. This observation will limit use of refrigerated fluids for TH induction, or at least delay their use until the patient has reached the hospital where potential complications can be more easily managed. Possibly, use of intranasal cooling, esophageal cooling or novel hypocarbon cooling pads could provide useful alternatives for pre-hospital cooling [11-13].

Attempts to lower or maintain temperature using external or internal cooling methods will be complicated by vigorous "countermeasures", i.e. attempts by the patient's body to raise core temperature through various mechanisms. Of note, these warming mechanisms are more active at temperatures that are closer to the hypothalamic "setpoint" in the brain, and usually decrease when core temperature drops below 34-34.5oC [4-5]. Therefore, technology that enables very rapid cooling may also decrease the shivering response [4]. Efficacy of cooling is also determined by factors including age (less effective vascular response, slower counter-regulatory response, and lower basal metabolic rate in older patients, making them easier to cool), body mass (more difficult to cool obese patients), and severity of brain injury (less vigorous/absent shivering response in very severe brain injury, facilitating cooling [3-5]; thus paradoxically, ease of cooling may predict poor outcome, especially with less effective cooling technology, whereas increased workload of cooling devices predicts better neurologic outcome [4-5,14].

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15.10 - 15.30 Future aspects of TTM: new cooling devices?
Kees Polderman, Pittsburgh (US)

Session 8: TTM - From Current Practice to Future Perspectives

15.30 - 15.50 TTM: biomarkers, neurophysiology, brain imaging
David Greer, New Haven (US)

Over 420,000 cardiac arrests occur yearly in the U.S., and over 275,000 in Europe.3-6 Mortality rates range from 60-85%. Most patients hospitalized remain unresponsive, and the extent of brain injury is the most critical factor for survival and recovery. An assumption of poor neurological prognosis commonly leads to withdrawal of life-sustaining therapy (WLST) and death. However, continued intensive care in patients with poor prognosis may commit them to lifelong institutionalization without an acceptable quality of life. Accurate prognostication is essential to guide decision makers, limiting the emotional and financial burdens associated with premature or extended care.

Prognostic techniques traditionally rely on findings from neurologic examinations and electrophysiology, such as electroencephalography (EEG) and somatosensory evoked potentials (SSEP). Advances in post-CA care such as targeted temperature management (TTM) have increased survival and have become standard of care, but have also led to prolonged effects of sedation, confounding the neurological examination in predicting outcome. This stresses the need for novel methods to assess the extent of injury not influenced by TTM. The current literature is flawed and biased7; collaborative efforts are essential to improve prognostication and outcomes in post-CA patients.8

For the time being, the absence of pupillary and corneal reflexes 72 hours post-arrest (or post-complete rewarming, if TTM has been utilized) continue to be reliable signs to predict poor prognosis, as well as absent cortical (N2) potentials on SSEP at least 48 hours post-arrest (or post-complete rewarming, if TTM has been utilized). Absent or extensor motor responses no longer appear to be reliable in the setting of TTM, nor does the presence of myoclonic status epilepticus. Few signs have correlated with good prognosis. EEG, particularly continuous EEG (cEEG) may provide great insights to pathology and recovery, and some advocate for aggressive anti-seizure treatment if seizures are detected. The reliability of such findings as reactivity and identical bursts on EEG need to be validated by prospective studies. Neuroimaging can and should be utilized for practical purposes, but again, their appropriate use has not be determined definitively and is not found in current guidelines.

Clinicians rely on EEG and neuroimaging to predict outcome after CA.9 However, these modalities are neither validated nor recommended for prognostication in societal guidelines.10,11 Furthermore, the timing of these tests has not been standardized, and potential confounders are not commonly controlled. Future studies need to incorporate high quality standardized data collection at exemplary sites with expertise for the multiple modalities used in outcome prediction, and efforts need to be made to avoid premature pessimistic prognostication leading to inappropriately early WLST.

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Session 8:	TTM - From Current Practice to Future Perspectives
15.30 - 15.50	TTM: biomarkers, neurophysiology, brain imaging David Greer, New Haven (US)

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15.30 - 15.50 TTM: biomarkers, neurophysiology, brain imaging
David Greer, New Haven (US)

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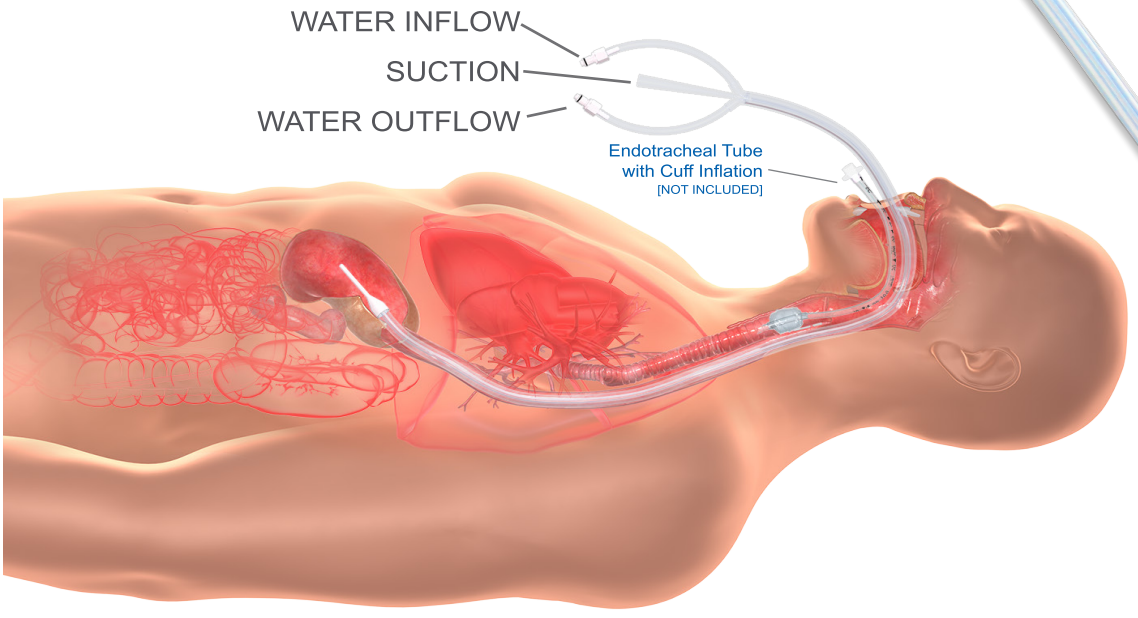

ECD-056 Rev D

The ECD is available for sale in Europe, Canada, Australia and the US.

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ZOLL Medical Deutschland GmbH
Bereich TMS
Emil-Hoffmann-Str. 13
50996 Köln

ZOLL International Holding B.V.
Newtonweg 18
6662 PV ELST
The Netherlands

ZOLL Medical Österreich GmbH
Twin Tower
Wienerbergstrasse 11
A-1100 Wien

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