Critical Care 2012, Volume 16 Suppl 2
http://ccforum.com/supplements/16/S2

CRITICAL CARE

MEETING ABSTRACTS Open Access

Update on therapeutic temperature management

Portoroz, Slovenia. 7-9 June 2012

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Published: 7 June 2012

These abstracts are available online at http://ccforum.com/supplements/16/S2

INTRODUCTION

A1

Update on therapeutic temperature management

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Critical Care 2012, **16(Suppl 2):**A1

It is a pleasure to announce the 2nd Innsbruck Hypothermia Symposium. We are very happy that *Critical Care* has agreed to publish extended abstracts submitted by invited renowned scientists from all over the world; that is, Europe, the Americas, Asia. Neuroprotection - potentially achieved by targeted temperature management (that is, therapeutic hypothermia or prophylactic controlled normothermia) - is essential in emergency and acute care management of various severe neurologic and cardiologic diseases. Beyond neuroprotection - for this aim, therapeutic hypothermia has been established after resuscitation of patients with cardiac arrest due to a shockable arrhythmia and in neonatal asphyxic encephalopathy - therapeutic hypothermia and prophylactic controlled normothermia have been published in single case reports, retrospective, open, but also in prospective randomised controlled trials in many other emergency disciplines in which both neuroprotection and protection of other organs and tissues are the target of our therapeutic endeavours. The Medical University Innsbruck, Austria, is happy to organise this conference on temperature management, therapeutic hypothermia and prophylactic normothermia respectively, to be held in Portoroz, Slovenia. In accordance with the first Meeting on Hypothermia, which was held in Miami, Florida, USA (CHilling At the Beach), we are proud to suggest the acronym CHAB standing for take Care for Heart And Brain, characterising the major target organs of therapeutic and, possibly also, prophylactic temperature management. Again, we have been able to gather most renowned scientists, neurointensivists and intensivists, emergency physicians, cardiologists and other specialists to cover the entire scientific and clinical spectrum of emergency temperature management, technical aspects of cooling and management of potential complications including shivering, but also temperature management in neurology, neurosurgery, intensive care medicine, in the operation theatre, cardiology, infectious diseases, and so forth. Beyond that we cross borders and discuss hypothermia and intracranial pressure, pharmacodynamics in hypothermic patients and the influence of hypothermia onto pharmacokinetics/pharmacodynamics, hypothermia in refractory status epilepticus or heat stroke, hypothermia and advanced neuromonitoring, hypothermia and nutrition, shivering and the critical issue of rewarming, amongst other topics.
The aim of this symposium is to enhance the knowledge on temperature management, increase the readiness and stimulate the preparedness to institute therapeutic hypothermia and/or prophylactic controlled normothermia, respectively, in patients in need of tissue and organ protection, uncontrolled body temperatures possibly adding - *per se* - to neuronal damage. Knowing the medical literature and knowing the issue of potentially life-threatening side effects and complications incurred by this invasive therapeutic manoeuvre, it is the foremost aim of this symposium and this supplementary issue of *Critical Care* to discuss all these aspects of targeted temperature management in emergency, critical care and, in particular, neurocritical patients and conditions. For this reason the organisers have agreed that the discussion of these various issues, being so important for general critical care, neurocritical care and emergency medicine, must be distributed as widely as possible, making it available to critical care and neurocritical care specialists all over the world. Therefore we are extremely grateful to the Editors of *Critical Care* for providing a forum for all of the extended abstracts of all invited speakers, covering the entire field of adult emergency and critical care medicine. We do hope and we are convinced that this supplementary issue will be a source of inspiration and knowledge, hopefully becoming a work of reference for intensivists, neurologists, neurointensivists, cardiologists and all emergency physicians alike. It is the aim of the organisers to establish a series of such symposia within the next years in order to keep up with all the developments in this field and to maintain the highest possible level of knowledge of targeted temperature management in the community of emergency and intensive care physicians.

EMERGENCY TEMPERATURE MANAGEMENT

A2

Therapeutic hypothermia: the rationale

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Critical Care 2012, **16(Suppl 2):**A2

For almost a century, therapeutic hypothermia - or as it was termed in the early days: hibernation - has been discussed as a potential neuroprotective measure, in particular in patients suffering from severe intracranial disease leading to impairment of consciousness, associated with fever [1-3].
In a wide range of diseases, secondary damage to the brain or other organs follows the initial impact and may be responsible for aggravation of disease condition or clinical state, in particular neurological morbidity and/or mortality [4-11]. Therapeutic hypothermia, recently renamed targeted temperature management, including prophylactic normothermia, has been used to improve this secondary impact onto brain and other organ tissue. This holds true, in particular, for neurological and neurosurgical intensive care patients since secondary brain and nervous tissue injury may preclude a potentially benign course of disease. The mechanisms of action of hypothermia are complex, not yet fully understood. Therapeutic hypothermia/targeted temperature management aims to attenuate a cascade of secondary injury mechanisms, which is started immediately

after the initial event (primary injury) and may last for hours and even days [4,6,12]. The majority of research has focused, so far, on these secondary injury processes being destructive to brain and nervous tissue. It may be expected that any such protective effect can be replicated in other organs and tissues during therapeutic hypothermia/targeted temperature management. A wide range of side effects may negate and counteract its positive initial effect; this implies side effects of hypothermia *per se* and side effects of rewarming or inconstant maintenance of temperature levels [13-17].

This abstract limits itself to potential pathophysiological mechanisms of actions, the risks of any such mechanism and side effects derived from them [4,5,10,12,16-18].

The protective effect of hypothermia may be explained by several pathways. A *decreased metabolism* with *less oxygen* and *energy consumption* and *carbon dioxide production* may prevent secondary injury when oxygen supply is interrupted or, at least, impaired. However, it needs to be stressed that the reduction in metabolic rate, as seen in hypothermia, requires adjustment in ventilator setup, insulin infusion rate, correct interpretation of electrolytes, in particular low phosphate, magnesium and potassium levels. Of particular interest are the rebound phenomena during rewarming or when, involuntarily, the temperature cannot be maintained at the targeted low level.

Following ischemia, hypoxia or direct trauma apoptotic processes may be initiated in brain tissue and neuronal cells may even become *necrotic*. In these earliest stages these pathways may be blocked by hypothermia. However, little is known about the time frame and best window of opportunity to use therapeutic hypothermia to prevent initiation of apoptotic/necrotic processes.

Any type of neuronal injury may provoke the *neuro-excitatory cascade*, starting off with excessive *calcium influx, glutamate receptor activation, neuronal hyperexcitability*, eventually leading to cell death even after reperfusion and normalization of glutamate levels. It has been suggested that therapeutic hypothermia may reduce cellular/neuronal damage following this neuro-excitatory cascade.

It has been accepted that the *release of free radicals* may be deleterious to both neuronal cells and the brain's defense mechanisms alike. Whether the direct impact or the ischemia reperfusion injury is overwhelmingly responsible for the release/increase of free radicals oxidizing and damaging neuronal cell components is both still a matter of discussion and of limited interest when therapeutic hypothermia comes into play.

Hyperexcitability, cellular hyperactivity, mitochondrial dysfunction, ion-pump failure and reduction in cellular membrane integrity may lead to intracellular and, consequently, also *intercellular/extracellular acidosis*.

Early initiation of hypothermia may improve this full spectrum of cellular failure, improve brain glucose and energy metabolism and reduce lactate accumulation; with this, intracellular and intercellular acidosis will improve and eventually metabolic recovery be enhanced [4,19-21].

Any type of brain injury is capable of *disrupting the blood brain barrier* leading to enhanced vascular permeability, brain edema, vascular permeability and perivascular hemorrhage. *Brain edema*, both after ischemia/hypoxia and traumatic injury peaks after 24 to 72 hours (sometimes reaching its highest peak even after this period of time) - thus opening widely the therapeutic window - allowing for therapeutic hypothermia to reduce brain edema via stabilizing the disrupted blood-brain barrier and vascular permeability. After brain injury *proinflammatory mediators are released*, leucocytes cross the - already impaired - blood-brain barrier leading to an *accumulation of inflammatory cells in the b*rain. This inflammatory response starts within 1 hour after injury and may persist for up to 5 days, a fact which also suggests a widely open therapeutic window for intervention. Hypothermia has been shown to reduce ischemia induced inflammatory and immune reactions [4,19-22].

In healthy persons, brain temperature is around 0.5 to 1°C higher than core body temperature. In any type of brain injury, in particular, in patients with fever or hyperpyrexia respectively, injured areas may be definitely hotter (up to 2°C post injury), most probably due to transitory cellular hyperactivity. Local brain edema might lead to cerebral thermopooling adding to *hyperthermia-related neuronal cellular injury* [4,16,18-21].

Cooling below 35°C has been shown to affect coagulation, it depends on the initial type of brain injury whether a procoagulatory effect or an anticoagulatory effect is believed to be neuroprotective in an individual case. Targeted temperature management may influence the secretion of vasoconstricting substances (for example, endothelin) or vasodilating substances (for example, prostaglandins). Their balance is essential to maintain homeostasis. Ischemic or traumatic conditions may increase vasoconstricting substances thus leading to reduced cerebral blood flow. Whether hypothermia is capable of regulating/improving cerebral perfusion is still a matter of investigation, pending the influence of cerebral autoregulation and the quantity of secreted vasoactive mediators in brain-injured patients with cerebral ischemia or any other type of injury [10].

Whether epileptic activity, in particular, subtle nonconvulsive status epilepticus, accepted to indicate severe brain damage, can be positively influenced by therapeutic hypothermia still needs further research. However, it is accepted that a subtle nonconvulsive status epilepticus occurring in the acute phase of brain injury is - *per se* - adding to neuronal destruction [10,16].

While many pathophysiological processes and cascades may be influenced by targeted temperature management/therapeutic hypothermia and/or even prevention of fever through prophylactic normothermia, it is unclear whether in all types of severely brain-injured patients (for whatever reason) the benefits of this therapeutic hypothermia always outweigh its risks. It is now fully accepted and of a high level of evidenced medicine that in cerebral hypoxia (in a patient with cardiac arrest due to a shockable arrhythmia) as well as asphyxial encephalopathy a 24-hour therapeutic hypothermia (33 to 34°C), irrespective of the type of cooling, improves neurological outcome; that is, morbidity but also mortality [7,10]. Whether therapeutic hypothermia/targeted temperature management or prophylactic normothermia may improve outcome in other diseases, as discussed in this meeting, is still not clear. It needs to be stressed that even such seemingly similar diseases as global hypoxia (in cardiac arrest due to a shockable arrhythmia), asphyxial encephalopathy and ischemic stroke have so few pathophysiologic cascades in common. Therefore, they may not be treated all alike, in particular, with respect to type, duration, speed and depth of hypothermia as well as rewarming management [23]. It has already been demonstrated that in hypoxic encephalopathy hypothermia for 24 hours may be sufficient. However, disease entities such as ischemic stroke, hemorrhagic stroke with formation of peri-hematomal edema, traumatic brain injuries with prolonged secondary insult or the wide range of neuronal injuries after subarachnoid hemorrhage may present even more complex pathophysiologic mechanisms. Moreover, different pathologies such as encephalitis and bacterial meningitis or even spinal cord injury may all require a targeted and personalized approach to this adjunctive therapy. In some cases, prolonged hypothermia may be equally necessary as in other cases mild hypothermia or even only prophylactic normothermia may suffice.

It may be stated beyond doubt that the neuroprotective effect of moderate hypothermia (33 to 34°C) has been shown in cerebral hypoxia and asphyxial encephalopathy. However, different neurocritical care disease entities as discussed above have different mechanisms of primary insults as well as the mechanisms and cascades of secondary brain injury and therefore require a different therapeutic approach in respect of temperature management.

Any type of therapeutic measure, still being the subject of research, must never harm the patient. Hypothermia-induced neurological signs and symptoms must never be misinterpreted and as a matter of course the diagnosis of brain death can never be confirmed under hypothermic conditions [24].

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A3

Prehospital hypothermia

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Critical Care 2012, **16(Suppl 2):**A3

Mild hypothermia is widely used in the treatment of successfully resuscitated patients after cardiac arrest [1]. Previous experimental and clinical studies have demonstrated beneficial effects of cooling after cardiac arrest. Two clinical landmark studies in 2002 demonstrated the use of therapeutic hypothermia after cardiac arrest due to ventricular fibrillation decreases mortality and improves neurological outcome [2,3]. This led the International Liaison Committee on Resuscitation and the American Heart Association to recommend the use of therapeutic hypothermia after cardiac arrest as soon as possible after the return of spontaneous circulation (ROSC) [4].

Despite major progress in intensive care medicine in the last decades, mortality rates after cardiac arrest remain unacceptably high [2,3]. The high mortality rates after cardiac arrest can be attributed to a unique pathophysiological process [1,5,6]. The entity of the pathophysiological changes after ROSC - for example, activation of the inflammatory system - can be summarized as the post-cardiac arrest syndrome [1,5-7].

Hypoxic encephalopathy, which is often a result of the initial hypoxic phase and/or the post-cardiac arrest syndrome, is one of the main causes for mortality, disability and a need for permanent care in patients after cardiac arrest [1].

Pathophysiologically, the resuscitation period could be divided into different time periods. After cessation of circulation, ischemia of different tissues leads to necrotic cell death (hypoxia-induced cellular dysfunction) [7,8]. Reperfusion injury then follows after an imprecise period of time once oxygenated blood is returned to the ischemic tissues with the beginning of mechanical resuscitation (reperfusion-induced cell death) [7,8]. From experimental and clinical studies, it is clear that the tissue damage due to reperfusion occurs over several hours to days in the post-resuscitation phase [1,7,8].

Several experimental studies have emphasized induction of therapeutic hypothermia as soon as possible after ROSC or during cardiopulmonary resuscitation [7-10]. These studies in the different animal models demonstrate a beneficial effect, including attenuation of the cerebral injury after prolonged ischemia due to earlier cooling [7-10]. Recent experimental data in different animal models of cardiac arrest, stroke and myocardial infarction suggest that warm reperfusion under normal or hyperthermic conditions could increase the deleterious effects of the reperfusion. For the effective prevention and treatment of the reperfusion injury, reperfusion should occur in temperature-controlled or cooled tissues.

Nevertheless, prehospital induction of therapeutic hypothermia is still under discussion; consistent protocols are not present and human data are rare. In a retrospective clinical study, early achievement of the target temperature appeared to reduce hypoxic brain injury and favor a good neurologic outcome after successful resuscitation [11].

On the other hand, a small retrospective, observational investigation found a faster decline in body temperature to the target temperature is linked to a less favorable neurologic outcome in comatose patients after cardiac arrest treated with therapeutic hypothermia [12]. However, this may simply indicate a severe ischemic damage with consecutive impaired thermoregulation [12].

In the PRINCE study, feasibility of preclinical transnasal cooling with evaporated perfluorcarbon that primarily leads to a prior selective cooling of the cerebrum was analyzed. In a subgroup of patients, intra-arrest hypothermia via evaporated perfluorcarbon was beneficial [13,14]. Several other studies show also safety and feasibility of prehospital hypothermia [15,16]. In summary, prehospital treatment of patients with a cardiac cause of the arrest may increase the rate of favorable outcome at hospital discharge. Further larger clinical investigations are needed to evaluate the effects of prehospital cooling in cardiac arrest patients [7,8]. In a small survey of emergency physicians in Germany, only a minority of patients is frequently treated with hypothermia before hospital admission after successful resuscitation [7,8].

However, taking the pathophysiological processes into consideration, induction of therapeutic hypothermia should not be limited to the ICUs but should also be able in the field or in the emergency department. Different methods are available to achieve and maintain the target temperature in the prehospital setting [7,8].

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A4

Standard operating procedures: therapeutic hypothermia in CPR and post-resuscitation care

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Critical Care 2012, **16(Suppl 2):**A4

After two randomised studies published in 2002 [1,2] mild therapeutic hypothermia treatment was internationally recommended as early and efficious treatment for comatose survivors after cardiac arrest (CA) not only with ventricular fibrillation, but also for patients suffering from CA presenting with other initial rhythms (asystole, PEA) and different underlying causes. Therapeutic hypothermia has been shown in these investigations to improve not only survival significantly after CA but especially the neurologic outcome after different courses of cooling treatment. Nevertheless the in-hospital mortality of those patients remained high.

While several prehospital or pre-CPR factors contributing to the patients' outcome are well known and implemented in the BLS and ACLS guidelines, only little is known about the kind and impact of in-hospital contributing factors worsening the chance of surviving the event with good neurological function. After return of spontaneous circulation, major cardiovascular and haemodynamic disorders are widely common and associated with a high rate of deaths within the first 24 hours after CPR. Sufficient post-resuscitation therapy has to include optimal treatment strategies of the cardiovascular and metabolic system, adaequate ventilation support and strategies of neuroprotection [3]. In patients surviving with a favourable outcome, haemodynamic and respiratory disorders tend to normalise within the first 24 hours after ROSC.

Several factors of hospital care are obviously important for survival of post-CA patients. Observational investigations done in Norway and Sweden detected severe differences in outcome of patients admitted to hospital with ROSC after out-of-hospital CA presenting survival rates between 33 to 56% and 14 to 42% respectively [4-6]. There were no significant differences in the prehospital management of those patients, but in-hospital factors like blood glucose levels, seizures, body temperature and laboratory changes could be related to outcome. A similar cohort study using a multicentre clinical ICU registry in the United States enrolled 4,674 patients from 39 hospitals covering a 4-year hiatus showed the same interhospital variability in survival with an unadjusted mortality ranging from 41 to 81%. Those patients treated in centres with higher case volumes were significantly less likely to die in-hospital after ROSC independent of the location of the CA. As it was not possible to differentiate the effect of specific therapies and interventions on survival in the post-CA period, the results underlined the need for additional research to define optimal post-cardiac treatment strategies. The data underlined not only the volume-outcome relationship but also the necessity of implementing standardised guidelines for optimal post-CA care in specialised centres.

Based on this evidence a prospective observational study was performed in patients admitted to hospital after regaining ROSC and treated using a standardised treatment protocol including instant onset of therapeutic hypothermia, early reperfusion treatment with PCI, and protocol-based early-goal-directed therapy to restore adaequate arterial blood flow in the reperfusion period [7]. The observational group from the interventional period was compared with controls from an earlier period in the same hospital. There were not only major differences in survival but also in the quality of neurologic outcome. After implementation of the standardised treatment protocol, survival improved from 31% to 56% in the interventional period, 56% of the patients showed a favourable neurologic outcome (26% in the control period) at hospital discharge and were still alive after 1 year. With no changes in the algorithm of prehospital care in the years of the investigation, post-resuscitation care appeared to have a major effect on improving not only survival but also the neurologic outcome after successful CPR.

Despite the fact that the level of evidence for many of the treatment strategies with the exception of therapeutic hypothermia in post-resuscitation care is weak, the quality of care after admission to the ICU or ED seems to be a somewhat missing link in the chain of survival. The post-resuscitation phase is associated with a sepsis-like syndrome [8] of unknown time course causing or even intensifying global ischaemic brain damage and dysfunctional heart disease. Treatment of these disorders is the main challenge after ROSC, but implementation of such strategies is often slow and in a heterogeneous manner causing a widely variable state of post-resuscitation care.

Many factors (Table 1) may contribute to this phenomenon and show the complexity of treating patients after ROSC. This underlines the necessity of using protocol-driven care in those patients to help physicians and nurses to raise the level for the number of patients receiving standard therapy. It is obvious that such protocols have to be adapted to local hospital specialities and logistic factors.

In our hospital an early algorithm for therapeutic hypothermia based on the standards used during the HACA trial [1] was designed and implemented immediately after enrolling patients for that European multicentre study in 2001. All patients being successfully resuscitated after CA independent from localisation, initial rhythm and type of the event were treated by therapeutic hypothermia and enrolled in our own database (CoolBrain Registry Bonn) including EMS data, course and technique of cooling and following temperature management, neurologic outcome at discharge and in a 1-year follow-up. Shortly after implementing the cooling protocol a special algorithm for general post-resuscitation care including therapeutic hypothermia and focusing on an early goal-directed approach to cardiac function, normoventilation, seizure treatment and strict avoidance of high blood glucose levels was designed and enabled physicians and nurses how to monitor and treat those patients. Baseline data of heart and brain function using invasive cardiac output monitoring and brain damage markers were included in the database as well. Both protocols and order sets are actualised to new guidelines and therapeutic standards based on actual science on a regular basis.

Table 1(Abstract A4) Inhospital factors influencing outcome of CA patients

Lack of implementation of therapeutic hypothermia and temperature management
Missing standard operating procedures/protocols for post-resuscitation care
Time lapse from ROSC to start of interventional phase
Treated case volumes of CA patients
Training and experience of personnel
Inadequate post-arrest treatment decisions

Unfortunately there is only limited access to outcome data of our patients treated before implementation of these SOP protocols, so the data from the CoolBrain Registry are only observational and cannot be compared with a control group before using protocol-driven therapeutic standards. Neurologic outcome was not recorded before implementing therapeutic hypothermia as standard care in 2001; survival rates after OHCA were recorded between 1990 and 2000 as lower than 20%.

Data enrolled from March 2001 to December 2011 (n = 276) presented a general survival rate of 51% independent of origin, initial rhythm and localisation of the cardiac arrest. Thirty-nine per cent of those patients showed a favourable neurologic outcome (CPC 0.5), 12% severe neurologic disability. In the group of survivors, 69.5% of patients with ventricular fibrillation as the initial rhythm showed an excellent neurologic performance (CPC 1) and 35% of patients presenting with asystole/PEA as well at hospital discharge.

Despite missing a control group before implementing therapeutic hypothermia and standardised treatment protocols for post-resuscitation care, these data show the effect of protocol-based treatment especially on neurologic outcome of those patients. This underlines that more attention has to be focused on optimising and standardising post-resuscitation care to improve survival and neurologic outcome. Treatment of patients with CA does not end with ROSC; despite the fact that there is only weak scientific level of evidence for some singular strategies of post-CA treatment, the combination of an aggressive multifactorial therapeutic approach including temperature management significantly improves outcome. Therefore further clinical trials of other post-resuscitation therapies seem to be essential.

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A5

In-hospital hypothermia

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Critical Care 2012, **16(Suppl 2):**A5

Introduction: Mild therapeutic hypothermia after cardiac arrest has become standard in post-resuscitation care in many hospitals as it is recommended by current guidelines. The last update of guidelines by the European Resuscitation Council on post-cardiac arrest treatment in 2010 recommends hypothermia for every patient after cardiac arrest who remains unconscious after cardiac arrest [1]. In addition to milestone trials [2-4], current published retrospective data from the large Finnish registry showed in a large group of patients a significant reduction of hospital mortality of survivors of out-of-hospital cardiac arrest after implementation of hypothermia [5].

The mild therapeutic hypothermia procedure after cardiac arrest can be divided into three phases: introduction, maintenance and rewarming. The cooling techniques and devices to induce cooling of the cardiac arrest survivor can be separated into three main groups: conventional cooling (no device), non-invasive (surface) systems, and invasive (intravascular) systems (Table 1).

Cooling techniques: Conventional cooling methods: The easiest way to induce hypothermia after cardiac arrest is by using cold saline (for example, 0.9% NaCl solution), crushed ice or ice bags. Kim and colleagues reported the safety and efficacy of the administration of up to 2 litres of 4°C cold saline to the patient after hospital admission [6]. Others published data using 30 ml/kg body weight of saline 0.9% NaCl or Ringer's lactate combined sometimes with ice bags, which led to an acceptable reduction of the temperature [7-10]. Furthermore cold saline as well as other methods like cooling caps and helmets have been evaluated for induction mainly in the preclinical setting [4,11,12]. Kliegel and colleagues pointed out that cold infusion alone is effective for induction but not for tight maintenance of the target temperature [13]. However, in at least one trial the combination of cold saline and ice packs was proven to be effective even to maintain temperature [7]. Focusing on the induction in the in-hospital setting, most authors rank cold saline and crushed ice more as effective adjuvant methods to be combined with a computer-controlled cooling device [10]. The big advantage of cold saline is its availability at almost every place in the hospital if provided and the low costs. Following the data available concerning different amounts of saline administered to the patient, a median amount of 1 to 2 litres of saline seems safe after cardiac arrest. To maintain target temperature with cold saline and ice bags seems to require a high binding of personnel method without a very precise influence on the central body temperature.

Surface cooling methods: Surface, non-invasive devices have to be distinguished from intravascular, invasive devices. The range of available computer-controlled surface devices with automatic temperature feedback stretches from cooling blankets to be placed around the patient (Blanketrol III, Cincinnati Sub-Zero; CritiCool, Medical ThermoRegulation Expertise) to adhesive cooling pads (Arctic Sun, Bard). Heard and colleagues compared the adhesive Arctic Sun surface-cooling system with normal cooling blankets combined with ice bags. Although the reached target temperature within 4 hours was not significantly different between the groups, the Arctic Sun system cooled more rapidly down to the target temperature [14]. A current investigation from Norway compared the Arctic Sun surface (C.R. Bard) system (n = 92) with the invasive intravascular Coolgard (Alsius) system (n = 75) in cardiac arrest survivors. The authors concluded no significant differences concerning neurological outcome and survival at discharge. A limitation for interpretation of the device efficacy (cooling rate/hour) is the additional induction of cooling with cold saline and ice bags already in the emergency room [15]. A published case report described a severe skin peeling during hypothermia with the Arctic Sun system without a known history of skin problems or steroid therapy but with end-stage renal disease and coronary artery disease. This is the first severe adverse skin event towards the hydrogel pads known and the authors conclude that these skin lesions are very unusual as to be caused by the adhesive pads because exfoliative dermatitis is a rare syndrome and is often drug induced [16]. Thus adverse skin reactions should not normally be expected using this method of cooling.

Another surface feedback system using blankets is the CritiCool Pro system by Medical ThermoRegulation Expertise (MTRE, Israel). The patient is wrapped into the body-shaped heat exchange garment resulting in a median cooling rate of 0.7 ± 0.37°C/hour in a study by Laish-Farkash and colleagues [17]. The Cincinnati Sub-Zero system has been compared with the ArcticSun2000 (C.R. Bard) system by Mayer and colleagues for fever control in neurocritical care patients. The authors conclude the ArcticSun system to be superior to the Cincinnati Sub-Zero system due to the maintenance of normothermia, a higher cooling rate and better fever reduction, although shivering occurred more frequently in the ArcticSun group [18]. A surface cooling system without computer control and automatic temperature feedback is the EMCOOLS cooling system. The adhesive pads use a novel carbon cooling gel that has a high thermal conductivity resulting in a cooling rate of more than 3.5°C/hour. The Flex Pad needs to be adapted to the body size and shape. The feasibility trial of out-of-hospital surface cooling after return of spontaneous circulation (ROSC) in 15 survivors using the EMCOOLS system revealed a high median cooling rate of 3.3°C/hour, the target temperature of 33°C was reached approximately within 70 minutes (55 to 106 minutes) after the start of cooling and no skin lesions were observed [19]. A further novel system is the Life Recovery ThermoSuit system, which was developed mainly for fast

Table 1(Abstract A5)

Company	Device	Type of cooling	Cooling rate (°C/hour)	Auto feedback	Reusable
Philips	InnerCool RTx	Catheter	4.0 to 5.0	Yes	No
Zoll	Thermogard XP	Catheter	2.0 to 3.0	Yes	No
C.R. Bard	ArcticSun 5000	Surface adhesive pads	1.2 to 2.0	Yes	No
CSZ	Blanketrol III	Surface blanket	1.5	Yes	Yes
EMCOOLS	FLEX.PAD	Surface adhesive pads	3.5	No	No
MTRE	CritiCool	Surface blanket	1.5	Yes	no

The table gives the most common cooling devices with no claim to be complete. Cooling rates provided either by the company or at the company's Internet homepage. CSZ, Cincinnati Sub-Zero; MTRE, Medical ThermoRegulation Expertise.

induction of hypothermia by cold water (2°C) immersion due to a lack of a temperature feedback mechanism. The water circulates continuously directly on the patient's skin with a median cooling rate of 3°C/hour [20]. Published data by Howes and colleagues report the safe use of the ThermoSuit system in 24 cardiac arrest survivors reaching the target temperature(<34°C) within 37 minutes (range 14 to 81 minutes) [21]. After the patients have reached the target temperature, they have to be removed from the suit and cooling maintained with other methods.

Endovascular cooling: Intravascular closed-loop cooling systems are also computer controlled with a temperature feedback. The Thermogard XP Temperature Management System (Zoll) provides both a central venous catheter with an additional closed loop balloon system with circulating water for cooling. The InnerCool RTx device (Philips) using the Accutrol catheter has a special feature with an integrated temperature sensor but no additional central intravascular access. A possible advantage of taking the temperature directly in the bloodstream is the avoidance of lag in core temperature measurement inherent in rectal and bladder sensors. The very precise temperature control is needed, taking the high average cooling rates of 4.0 to 5.0°C/hour into consideration. This cooling system will be under evaluation in the Rapid Endovascular Catheter Core Cooling combined with cold saline as an Adjunct to Percutaneous Coronary Intervention for the Treatment of Acute Myocardial Infarction (CHILL-MI) study. This study was started in 2012 to further investigate the safety and effectiveness of the endovascular cooling system in patients suffering from ST-elevation myocardial infarction (STEMI) and to confirm the data from the Rapid-MI-ICE trial [22]. In a subanalysis of the European Hypothermia After Cardiac Arrest trial (HACA), Holzer and colleagues retrospectively reviewed the efficacy and safety of the intravascular catheter system (Cool Gard 3000, Alsius) in 56 patients, revealing a cooling rate of 1.2°C/hour (IQR 0.7 to 1.5) without significant differences to other techniques concerning adverse events [23]. A study by Gillies and colleagues reported a good temperature control with endovascular cooling compared with conventional ice surface cooling [24]. After induction of cooling with cold saline, one group was continued to be cooled with ice (n = 41) whereas the other group was cooled with the Coolgard device (n = 42; Alsius). In summary, catheter cooling provided a more precise temperature control, better control during rewarming, less overcooling and failure to reach target temperature. Despite these advantages there was no difference concerning outcome between both relatively small groups [24]. The duration of time an intravascular catheter can be used as central intravenous access after rewarming is not well investigated so far. Al-Senani and colleagues evaluated the safety of the Icy catheter during a cooling procedure [25]. However, intravascular catheters can cause bloodstream infections and raise the question about the risk of venous thrombosis. Few cases with thrombosis or thrombophlebitis due to a cooling catheter after a using time of respectively 7 and 10 days have been published [26]. Simosa and colleagues reported in a group of 10 patients with traumatic brain injury that five patients developing a depth venous thrombosis after an average of 5.4 days but concluded that the group under examination already had a high risk for development of thrombosis due to lack of prophylactic anticoagulation [27]. However, the approach towards anticoagulation will be different in survivors after cardiac arrest. The recommendation for the duration of use of the Icy catheter is 4 days (Icy Quattro) but a novel surface coating of the catheter material will soon be approved by authorities to enhance time of use and decrease risk of thrombosis. In addition there might be a higher risk of developing catheter-related bloodstream infections but currently no data are published studying temperature management catheters and infection rates.

Other cooling methods: The novel RhinoChill intranasal cooling device was able to demonstrate effective reduction of body temperature within the Pre-ROSC Intranasal Cooling Effectiveness trial (PRINCE trial) [28]. The portable system vaporises perfluorchlorcarbon gas with a catheter system into the nasal cavity leading to a fast induction of hypothermia first to the brain as main target organ and second to the body with a slight delay. The intra-arrest cooling approach of the study, starting induction of hypothermia already during CPR, by Castrén and colleagues was conducted as a safety and feasibility study [28]. However, benefit towards survival and neurological outcome was observed in the cooling subgroup, having received CPR within 10 minutes after collapse, although the design of the study was not conceived for outcome analysis. The randomised trial compared in detail prehospital trans-nasal cooling (n = 83) with advanced cardiac live support (n = 99) and both groups received mild hypothermia on admission to the hospital regardless of the initial rhythm. This method was able to show a significant decrease of tympanic temperature on arrival (34.2°C vs. 35.5°C). Due to the convincing data from the PRINCE trial, the Prehospital Resuscitation Intra Nasal Cooling Effectiveness Survival Study (PRINCESS) started in June 2010 with patient recruitment and is designed to evaluate for good or poor neurological outcome and survival as well as to evaluate the proportion of those achieving ROSC and time to target temperature of 32 to 34°C. First data will be available in June 2013 (ClinicalTrial.gov identifier: NCT01400373). The system has no temperature feedback and the major application area is the induction of hypothermia. Another novel approach is under investigation in the CAMARO trial (ClinicalTrials.gov identifier: NCT01016236).

Following the idea of early and fast induction of hypothermia to improve outcome and decrease side effects after cardiac arrest and incorporate novel data that hypothermia applied before a coronary intervention may reduce the infarct size in STEMI patients, a new automated peritoneal lavage system (Velomedix Inc., Palo Alto, USA) has been developed [22]. The CAMARO trial includes cardiac arrest patients as well as STEMI patients who will be cooled to a target temperature of 34°C without prior resuscitation. The preliminary data of this pilot study, presented as an abstract at the American Heart Association Meeting in Orlando, USA, in November 2011, showed a decrease of temperature to 34°C within 9 minutes, the maintenance phase of 32.5°C was 24 hours in cardiac arrest patients (rewarming 16 hours) and 3 hours maintenance in myocardial infarction patients (rewarming 5 hours). At the moment no device-related complication has occurred with this extremely rapid cooling method [29].

Discussion: Different cooling methods with varying technical approaches and efficacy are available to deliver mild therapeutic hypothermia to our patients. During cooling the three phases of induction, maintenance and rewarming can be defined. Are different methods necessary to fulfil the requirements in each of these three cooling phases? Taking all mentioned methods together, a combined approach seems to be the optimal way. Particularly with regard to the induction phase a combination of different methods should be suggested to increase the effectiveness of cooling, for example the combination of cold saline and a feedback cooling device, although the optimal overall timing (time to target temperature and cooling rate) is still under debate. In addition to timing, the most important question concerns shivering and its prophylactic successful treatment.

The optimal and most beneficial time point to start hypothermia after cardiac arrest is still not known. The current European resuscitation guidelines recommend starting hypothermia as soon as possible after ROSC.

A recently published article by Sendelbach and colleagues revealed the importance of avoiding any time delay of cooling to reach good neurological outcome [30]. This 'earlier is better' strategy can be confirmed by animal data [31-34]. Following the 'earlier is better' strategy, some trials explored the possibility of inducing cooling during resuscitation or directly after ROSC, but data are controversial [35]. Induction of therapeutic hypothermia during prehospital CPR using ice-cold intravenous fluid or intranasal cooling showed that it is feasible and is partially a benefit [28,36]. A major problem in predicting outcome and association with timing and early cooling after cardiac arrest or even during resuscitation with these data is the small sample size and the fact that prehospital hypothermia was discontinued after admission to the hospital in many of these trials [37]. However, the analysis of data from the Scandinavian Hypothermia Network including 986 patients after cardiac arrest by Nielsen and colleagues showed no association of timing towards neurological outcome [38].

Certainly every ICU should provide 4°C cold saline to increase the cooling rate and to reach the target temperature as soon as possible. The administration of cold saline seems a feasible method in the preclinical setting as well as in addition to other preclinical devices available and after admission cold saline can be combined with a feedback device to speed up the cooling. Furthermore, shivering is one of the most important side effects that can occur during hypothermia leading to an increased metabolic rate, high oxygen consumption and heat generation, and therefore needs to be kept in mind to be avoided and treated aggressively. The threshold for this defence mechanism of the thermoregulatory system is around ±35.5°C (1°C below the vasoconstriction threshold) [39,40]. Therefore a fast induction to cross this threshold as quickly as possible seems indicated; additional treatment can include a sufficient analgosedation, magnesium and paralysation, but even the simple method of keeping the hands and feet warm by wearing socks and gloves directly from the beginning of induction of hypothermia can avoid shivering very reliably [41]. In patients with traumatic brain injury undergoing temperature management, the benefit of surface counter warming concerning less shivering and improvement of metabolic profile was reported [42]. However, a high cooling rate during induction with a combination of a feedback-cooling device and several additional conventional cooling methods in combination with hand and feet counter warming as described and a sufficient sedation level seems to be the best way to avoid shivering. In addition, every temperature management procedure requires a reliable core temperature. The gold standard is still the temperature taken directly in the bloodstream (for example, pulmonary catheter) or directly by the cooling device itself as possible with the Philips Accutrol endovascular catheter. Other common places for temperature measurement are the bladder by Foley catheters, oeosophageal probes, tympanic and rectal temperature [43]. Modern temperature management systems with high cooling rates lead to a fast induction of hypothermia that can only be detected by most temperature sensors with a time delay. The closed approach towards the gold standard might be the oesophageal measurement with an approximately average time delay of 5 minutes (range 5 to 10 minutes) [40].

Conclusion: A wide range of conventional and technical methods exists to apply mild therapeutic hypothermia after cardiac arrest. Hoedemaekers and colleagues compared all described different methods (conventional cold infusion/ice, water blankets, gel-coated pads, intravascular) in ICU patients regarding the speed of cooling (°C/hour) and the reliability to maintain a stable target temperature. The authors conclude that water-circulating blankets, gel-coated pads and intravascular cooling are almost equally efficient for induction but intravascular methods were superior for maintaining the target temperature [44]. Some performance data might have changed over the last years due to the industry having developed the next generation of cooling devices. However, every method has its own partly limited, indication and a combination of an automatic computer-processed feedback device with conventional methods seems a good and safe solution. The type of feedback device used in a hospital (invasive vs. non-invasive) depends on several factors but mainly on the personal preference of the treating doctors, type of patients and the local standard as well. In addition, the way of thinking is changing and it is no longer a question of making the patient cool as good as possible but rather has evolved into a complex temperature management procedure with its own risks and pitfalls as well as benefits for the patient. It is a precondition to ensure a precise and tight temperature control during all three treatment phases. Especially during rewarming, which is a very critical phase of temperature management, close temperature monitoring is necessary and can be easily achieved with a computer-feedback cooling system. A passive, uncontrolled increase of temperature should be avoided in the modern temperature management approach. However, the adoption rate and implementation of hypothermia as part of standard post-arrest care is still not high enough. Reasons are manifold but the latest version of available cooling devices may be able to help to increase the application rate by making the treatment safe and easy. If the hospital team feels confident with the topic of temperature management, numbers of operators might increase, even if the number of cardiac arrest patients treated in a hospital is low.

The presentation of different temperature-management methods and interpretation of their efficiency in the age of daily breaking news about mild hypothermia treatment and widening of the indication can only be a momentary snap-shot and cannot aspire to completeness.

Competing interests: The author received financial support and material resources from Medivance, Zoll, Philips, EMCOOL and C.R. Bard within different projects and honorarium from Medivance, Zoll and Philips for lectures. This abstract has not been influenced by anyone in collection of data, analysis, interpretation and writing.

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Pharmacodynamics in hypothermia

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Critical Care 2012, **16(Suppl 2):**A6

Introduction: Guidelines for using inotropic drugs to support cardiovascular function at low core temperatures are not well characterized. The safe application of inotropic drugs during normothermic conditions, routinely used to treat cardiovascular instability by effectively increasing cardiac output (CO) and improve end-organ perfusion associated with acute heart failure [1], is based on a detailed understanding of pharmacodynamics and pharmacokinetics of these drugs. Detailed knowledge of temperature-dependent changes in pharmacodynamics and pharmacokinetics of such cardioactive drugs is essential for establishing treatment guidelines.

Therapeutic hypothermia: Over the last decade therapeutic hypothermia has been established as a recognized intervention to increase survival and improve neurologic outcome in adult comatose cardiac arrest survivors [2-6]. However, after return of spontaneous circulation (ROSC) and coronary revascularization, more than 50% of survivors suffer from acute heart failure and need inotropic cardiac support to resume adequate circulatory function [2] after induction of hypothermia when the core temperature is deliberately lowered to 34 to 32°C and maintained for 24 to 48 hours. In contrast, in patients hospitalized for acute heart failure without hypothermia a subgroup of about only 10% received inotropic drugs [7].

Accidental hypothermia: Another group of patients in need of inotropic drug therapy at low core temperature are accidental hypothermia patients displaying hypothermia-induced cardiac failure during rewarming, ranging from mild reduction of CO to the fulminant circulatory shock termed rewarming shock [8-11]. Rewarming shock is a clinically descriptive term that refers to a pathophysiologic state of cardiovascular collapse taking place during or after rewarming from accidental hypothermia [12], recognized as a progressive reduction of CO and a sudden fall in arterial blood pressure. In order to treat or prevent rewarming shock, cardioactive inotropic drugs are commonly necessary to elevate a low CO.

Research in experimental hypothermia has displayed a substantial depression of LV myocardial function in earlier studies [8,11,13] as well as

in recent studies [9,13,14]. Based on the results from these studies, cellular calcium overload, disturbed calcium homeostasis, changes in myocardial myofilament responsiveness to intracellular calcium as well as impaired high-energy phosphate homeostasis could all be proposed as important factors leading to the changes observed in the hypothermic heart and contributing to failure of functional recovery during rewarming [15-18].

β-receptor agonists: In the acutely failing heart postoperatively, only drugs such as epinephrine and NE provide positive inotropy and perfusion pressure. Epinephrine acts through stimulation via sarcolemmal β-adrenoceptors, causing phosphorylation of the sarcolemmal L-type Ca^{2+} channel via cyclic AMP and protein kinase A pathways. This phosphorylation increases the open probability of the channel [19], allowing for greater trans-sarcolemmal Ca^{2+} influx with each depolarization and producing, in part, the positive inotropic effect of epinephrine.

Vascular effects: Only a few experiments studying effects of epinephrine during hypothermia or/and rewarming using *in vivo* animal models have been published. Some authors report that both β_1-adrenoceptors and α-adrenoceptors increase their sensitivity to catecholamines during hypothermia [18,20-22] as β_1-adrenoceptor activity was potentiated by low temperature, and they claim the existence of hypothermia-induced supersensitivity and increased agonist activity for β_1-adrenoceptors. In support of this view, a left shift of the concentration-response curve for epinephrine during hypothermia has been reported [23]. However, others suggest hypothermia-induced increase in sensitivity for both α_1-adrenoceptors and α_2-adrenoceptors during cooling [24], but that sensitivity of β_1-adrenoceptors is not increased to the same extent as α-adrenoceptors. In contrast, other researchers have reported a hypothermia-induced supersensitivity of β_1-adrenoceptors [18,20,21]. Rubinstein reported that hypothermia modified the vascular response to epinephrine [25]; that is, the epinephrine doses that induced vasodilation during normothermic conditions increased TPR at 25°C. He also claimed that myocardial contractile effects of epinephrine is reduced at low temperatures (covered below), a view also supported by others [25,25-27]. Experimental data show that the sympathetic nervous system could be switched off at a threshold temperature about 29°C and hypotensive patients with temperatures below this may benefit from infusions of exogenous catecholamines [28]. In addition, if CO could be elevated pharmacologically, rewarming by any means becomes more efficient [17,29]. Some researchers recommend infusion of low doses of catecholamines in patients who have lower blood pressure than would be expected for that degree of hypothermia and who are not responding to crystalloids and rewarming [29].

It therefore seems that the use of vasoactive drugs during hypothermic conditions remains quite contradictory.

Cardiac effects: Some sources claim that the hypothermic heart is unresponsive [30] or little responsive [31] to cardioactive drugs, and the last reference as well as recommendation of the American Heart Association [26] refer to the potential hazard of overmedication, due to delayed drug metabolism leading to accumulation to toxic levels in patients suffering from deep or severe hypothermia, if used repeatedly. The AHA recommends the following algorithm for treatment of hypothermia: below 30°C i.v. epinephrine should not be given, but above 30°C epinephrine should be given, if indicated, but at longer than standard intervals. To date, there are no prospective clinical studies to support the recommendation to avoid epinephrine during hypothermic CPR, but a preclinical work report major side effects of repeated epinephrine administration during experimental hypothermic CPR in pigs [32]. Even in the last recommendations from the AHA it was stated that treatment of severe hypothermia (temperature <30°C) in the field remains controversial [26].

A reduction of CO and SV by inducing varying levels of hypercalcaemia during hypothermia (28°C) was reported by Schiffmann and colleagues [18]. Following infusion of epinephrine during these experimental conditions, CO and SV were even more depressed [18]. These findings shear similarities with findings in our intact animal models: infusion of epinephrine, which theoretically will induce opening of Ca^{2+} channels, increase calcium influx and elevate intracellular calcium even further, caused a significant depression of myocardial function during hypothermic as well as post-hypothermic conditions [13,33,34]. This made us conclude that hypothermia and rewarming may cause alterations in the pharmacodynamic effects of α-receptor and β-receptor mediated drugs [13,33,35-37] or induce changes in receptor affinity for these drugs. Further, we found that low-dose epinephrine managed to maintain positive inotropic effects on LV cardiac function during cooling to 30°C, but these effects vanished during cooling to 28°C. If the epinephrine dose was increased at these low temperatures SV and CO were not elevated but a significant increase in afterload took place. Thus we conclude that if epinephrine is applied during hypothermia the therapeutic window appears narrow with short distance to unwanted side effects. Further, the prehypothermic dose-dependent increase in LV function in response to epinephrine was not present after rewarming in the group that had received epinephrine during hypothermia [13,33,35,38], and if epinephrine was infused during rewarming vascular side effects of epinephrine (vasoconstriction) dominated [13,38] without elevating CO above pre-hypothermic control values at any temperature.

During cooling there is a reduction in Ca^{2+} sensitivity of troponin C due to protein kinase A (PKA)-induced phosphorylation of troponin I [39], in addition to the hypothermia-induced calcium overload [18,19]. Further, it is documented that PKA may inhibit the activity of adenylyl cyclase (AC) 5 [40,41], predominantly expressed in the heart [42], which catalyzes ATP to cAMP. Based on this information, it is possible that lack of positive inotropic effect on cardiac function of β-receptor stimulation during hypothermia may be due to the inhibitory effects on AC 5 activity of PKA phosphorylation and/or a potential desensitization and internalization of the β-adrenoceptor. Another way of interpreting these results is that the efficacy of signal transduction through G-protein coupled receptors is rapidly decreased through mechanisms like desensitization and internalization, mechanisms that will avoid receptor overstimulation. However, during pathologic conditions, like acute heart failure following acute coronary syndromes and cardiac standstill, or as a consequence of exposure to accidental hypothermia, it is necessary for cardiac myocytes to produce cAMP over the limitation of such adaptations.

Dopamine: The still widespread use of DA in perioperative and intensive care, the explicit recommendation for its use in accidental hypothermia guidelines, and possible positive effects in hypothermia as reported from experimental studies all need evaluation. From experimental hypothermia research we found that DA improved both systolic and diastolic function in hypothermia [43]. However, at 25°C no beneficial effect was seen on CI as SI decreased with incrementing DA dosages. Increased SVRI at high-dose DA at 25°C suggests α-adrenergic involvement not seen in normothermia. Properties of the low-flow, high-viscosity circulatory state, combined with serious alterations in the pharmacokinetics of DA, may explain lack of beneficial - and potentially harmful - effects from DA administration at 25°C.

Milrinone: Milrinone is a phosphodiesterase (PDE) 3 inhibitor that is dominantly expressed in the heart and vascular tissues. The site of action of milrinone is cytosolic, and the administration of a PDE3 inhibitor increases cAMP only in the cardiovascular system, which subsequently enhance cardiac contraction and induce vasodilation during normothermic conditions [44]. In a recent experiment [45], using milrinone as a model drug of intracellular mode of action, the positive cardiac effects of this drug was demonstrated during normothermic conditions (30% increase in SV and CO) and remained during cooling to 15°C. These effects of milrinone on cardiac function stay in essential contrast to those in our previous studies testing effects of α-receptor and β-receptor mediated drugs [35,38] during cooling and rewarming.

Conclusion: Taken together, the use of cardioactive drugs during hypothermic conditions remains quite contradictory. Therefore, pharmacologic treatment applied during the clinically challenging modalities, therapeutic as well as accidental hypothermia, call upon written treatment protocols or guidelines that are so far largely missing or at least not properly updated. More research is needed to explore temperature-dependent changes in pharmacodynamics and pharmacokinetics of cardioactive drugs to write these guidelines. Thus, due to significant hypothermia-induced alterations of cardiac as well as vascular adrenoceptor sensitivity, the use of cardioactive agents not affecting these receptor systems are advised during hypothermic conditions.

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HOT AND COLD

A7

Pathogenetic mechanisms of heatstroke and novel therapies

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Critical Care 2012, **16(Suppl 2):**A7

Heatstroke, a life-threatening condition defined by a rapidly increasing core temperature greater than 40°C and multiple organ system dysfunction, is a leading cause of morbidity and mortality during heat waves [1]. The heat wave that affected Europe during August 2003 led to an unprecedented 70,000 excess deaths of which up to 40% were confirmed to be due to heatstroke [2]. Sophisticated climate models predict increasing frequency and severity of heat waves and so the incidence of heat-related death could rise if proactive measures and novel therapy to address this threat are not adopted [3].

The mechanisms of multiple organ system dysfunction in heatstroke are not fully understood and include direct tissue injury and cell death resulting from heat cytotoxicity together with delayed organ dysfunction and damage secondary to activation of inflammatory and coagulation pathways. Histopathological changes include endothelial injury, disseminated intravascular thrombosis, neutrophils infiltration and apoptosis [4,5]. Despite cooling and optimal treatment in intensive care the overall mortality from heatstroke exceeds 60%, due in large part to the fact that no specific treatment is available [6,7].

Experimental evidence from rodent models of heatstroke suggest that immunomodulation of the host response may alter the clinical course of

heatstroke and thereby improve outcome [8-10]. Heatstroke in induces systemic and local (central nervous system) production of TNFα and IL-1, and severe coagulopathy. This is associated with multiple organ system dysfunction including severe neuronal injury, and high mortality. Administration of an IL-1 receptor antagonist [8], corticosteroids [9] or activated protein C [10] before the onset of heatstroke attenuates the multiple organ system dysfunction and improves survival. However, extrapolation of these data from these small animal models to humans is problematic because of inter-species differences.

Baboons represent the most appropriate model for the study of the host inflammatory and hemostatic responses to heat stress and their relation to cellular injury and death as well as for testing novel therapy, which targets these pathways. Moreover, the findings may have direct applicability to human heatstroke, and could represent the basis for clinical trial. In this review, we show that baboons subjected to heat stress reproduce both the clinical and immunological changes similar to those seen in humans [11]. Using this experimental model, we report that immunomodulating the host systemic inflammatory and coagulation responses failed to translate into improved survival, suggesting that further basic research on the pathogenesis of heatstroke is required [12-14].

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A8

Is therapeutic hypothermia immunosuppressive?

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Critical Care 2012, **16(Suppl 2):**A8

Introduction: The answer to the question in the title of this article would appear obvious. Even the term 'to catch a cold' is partly based on the widely-held assumption that lower temperatures or a chill can decrease the resistance to certain viral infections such as the common cold [1]. Furthermore, a number of studies have clearly demonstrated that inadvertent decreases in temperature in the perioperative setting, and in some other situations, can significantly increase infection risk.

However, the question is not as easy to answer in cases where hypothermia is applied deliberately and with various precautions, which is the case in therapeutic cooling. In these cases potentially harmful responses such as shivering and tachycardia are carefully controlled, body temperatures are not allowed to drop below a predefined setpoint, and every effort is made to prevent side effects [2,3]. Moreover, even the evidence that hypothermia plays a role in the development of the common cold is mixed, and the few studies performed to address this issue did not support the popular belief that colds are associated with exposure to a cold environment [1,4].

The relationship between hypothermia and immune function are briefly discussed below.

***In vitro* studies and animal experiments:** In most types of acute brain injury there is a significant and protracted inflammatory response in the hours following the acute event, whether this is ischemic, traumatic, or a combination of both. Proinflammatory mediators such as TNFα and IL-1 are released in large quantities by astrocytes, microglia, and endothelial cells following an episode of ischemia and reperfusion [2]. The levels of these mediators begin to rise around 1 hour after injury and remain elevated for up to 5 days [2,5,6]. This in turn stimulates the chemotaxis of activated leucocytes across the blood-brain barrier and leads to an accumulation of inflammatory cells in the injured brain, as well as the emergence of adhesion molecules on leukocytes and endothelial cells. Simultaneously activation of the complement system occurs, beginning in the very early stages after brain injury. This further stimulates the passage of neutrophils and (in later stages) monocytes/macrophages [6]. These inflammatory and immunological responses occur especially during reperfusion and are accompanied by free radical production (see below). These inflammatory responses can cause significant (additional) injury through the phagocytic actions of macrophages, synthesis of toxic products, and further stimulation of immune reactions in a vicious cycle.

Thus it can be argued that, at least in the initial stages of acute brain injury, a hyperinflammatory state exists. As explained in some more detail below hypothermia attenuates this proinflammatory state, but this in itself does not constitute immune suppression. On the other hand, it should be realized that the proinflammatory response outlined above is to some extent physiological; there is evidence suggesting that some inflammatory mediators have neuroprotective properties, although many others are neurotoxic [6-9]. Thus attenuating the response could have protective effects, but also some detrimental ones [2,8,9].

On balance there is persuasive evidence suggesting that the production of cytokines and leukocyte infiltration is disproportionate and harmful, and can significantly increase the risk and extent of brain cell injury and infarction [6-15]. Especially, the IL-1 family appears to be important in this regard [15]. The destructive aspects of inflammation appear to outweigh the potential benefits especially in the later stages of injury [2,6-9]. Thus there is a potential time window for therapeutic interventions to block or mitigate this process before it causes permanent injury.

Many animal experiments and *in vitro* studies have shown that mild hypothermia can suppress harmful inflammatory reactions that damage potentially viable nerve cells and astrocytes [10-12]. Hypothermia can also decrease production of leukotrienes and nitric oxide, prevent reperfusion-related DNA injury and lipid peroxidation, and impair neutrophil and macrophage function [2,3]. Thus on balance the protective effects of cooling are likely to outweigh the potential negative effects. However, this does not mean that there are no negative effects, especially if the temperature drops below 32°C. It should be kept in mind that the suppression of inflammatory responses will occur in all organs, not just the injured ones; this is one of the reasons why inhibition of the immune response can lead to increased infection risk. Moreover, the effect is present regardless of whether a local or general hyperinflammatory state exists.

The systemic effect on the immune system can be enhanced by a decrease in the white blood cell count, which can begin at temperatures below 32 to 33°C (although major decreases usually occur only at temperatures below 30 to 31°C). Biggar and coworkers reported a drop in WBC count from 6.0 ± 0.6 to 2.3 ± 0.3 when hypothermia of 29°C was induced in pigs [16]. They did

not observe significant changes in the number of circulating mature or immature neutrophils, and reported that neutrophil demargination after administration of intravenous catecholamines was similar at 37°C and 29°C. However, they also observed that administration of corticosteroids and, importantly, of endotoxins failed to stimulate the normal release of neutrophils from the bone marrow [16]. Failure of this response could significantly impact infection risks [2].

Most of these observations were made in animal experiments, but the hypothermia-induced suppression of the hyperinflammatory responses and decrease in WBC count have been confirmed in clinical reports in humans with traumatic brain injury [10,11,17].

Thus the very mechanisms that provide tissue protection could simultaneously impair the patients' ability to fight infections. In addition, lowering body temperature can lead to a decrease in insulin secretion and to induction of insulin resistance [2,3]. This can lead to hyperglycaemia, which can in turn impair leucocyte function and further increase infection risks. Finally, hypothermia can cause vasoconstriction in the skin, which could increase the risk for bedsores and surgical wound infections.

In summary, based on the *in vitro* evidence we would expect hypothermia to inhibit the mostly harmful neuroinflammatory response and ameliorate the hyperinflammatory state that occurs after acute injury, but at the price of increasing infection risk.

Clinical evidence: Clinical studies reporting the infection risks associated with therapeutic cooling in different categories of patients with acute brain injury have produced divergent results; studies in patients who develop *accidental* hypothermia have mostly reported higher infection risks.

The link between accidental hypothermia in the perioperative setting and a higher incidence of surgical wound infections was first demonstrated by Kurz and coworkers in 1996 [18], and has since been confirmed in numerous studies in various categories of surgical patients [19-26]. The most recent example is a study by Seamon and coworkers, who found that intraoperative hypothermia (below 35°C) was independently associated with surgical site infection rates after trauma laparotomy [26]. Local factors such as hypothermia-induced vasoconstriction in the skin may add to the underlying immunosuppressive effect to further increase the rate of wound infections. Recently, Laupland and colleagues reported that severe hypothermia (<32°C, but not 32 to 35.9°C) was associated with significant increases in risk for infections acquired in ICU [27].

The link between hypothermia and infections is far less clear when mild hypothermia is induced under controlled circumstances. Numerous studies in patients with post-hypoxic brain injury following cardiac arrest have not reported significant increases in rates of infections, although some have reported trends in that direction [28]. Seven multicentered trials in newborn babies treated with neonatal asphyxia for 48 to 72 hours also did not report consistent increases in infection risks [28].

In contrast, clinical studies in patients with ischemic stroke and TBI have tended to find higher risks of infection, especially pneumonia, in patients treated with hypothermia. For example, Hemmen and coworkers reported a rate of pneumonia of 50% in patients with ischemic stroke treated with hypothermia and thrombolysis, compared to 10% in controls [29]. Although the overall outcome was better in hypothermia patients in spite of the high infection rate, this indicates that use of hypothermia in these patients may present significant difficulties.

Some studies using hypothermia in patients with severe traumatic brain injury have also reported high infection rates [28]. There is evidence that this can be prevented by a combination of preventive measures, perhaps including use of antibiotic prophylaxis such as selective decontamination of the digestive tract (SDD) [28,30,31].

In one example, Kamps and coworkers reported on their use of prolonged therapeutic cooling to control intracranial pressure in patients with severe traumatic brain injury, in a setting where SDD was routinely used, and reported that infection rates were 20% in patients treated with hypothermia and 34.4% for matched controls [31]. Most notably, the risk of ventilator-associated pneumonia was the same in patients treated with hypothermia compared with matched controls.

Conclusion: Hypothermia impairs immune function and inhibits various inflammatory responses. This is inherent to the treatment, and impairment of harmful inflammatory reactions in the brain may be one of the mechanisms through which hypothermia can exert protective effects. Hypothermia-induced insulin resistance and hyperglycemia may further increase infection risks. In clinical studies, hypothermia has been most clearly linked to infection risk in the context of accidental hypothermia; controlled therapeutic cooling appears to carry a lower risk, especially if hypothermia is used for limited periods of time (<48 hours). The risk appears to increase with prolonged use, and careful monitoring is required in these patients. Prophylactic antibiotics may be considered in high-risk patients who are cooled for prolonged periods.

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A9

Shivering: scores and protocols

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Critical Care 2012, **16(Suppl 2):**A9

Shivering is both an anticipated consequence and, potentially, a major adverse effect of therapeutic hypothermia. Even mild hypothermia can elicit a vigorous thermoregulatory defense to maintain body temperature at the hypothalamic set point. In healthy humans, peripheral vasoconstriction is triggered at 36.5°C and shivering at 35.5°C. Temperature thresholds for vasoconstriction and shivering are often higher than normal in brain-injured patients; therefore, these thermoregulatory defenses may occur more vigorously and at higher temperatures in these individuals. Control of shivering is essential for effective cooling, as shivering fights the cooling process, makes attaining target temperature difficult, is extremely uncomfortable, and can trigger massive increases in systemic and cerebral energy consumption and metabolic demand. The first step in treatment is adequate tools to recognize shivering. The Bedside Shivering Assessment Scale is a simple, validated four-point scale that enables repeated quantification of shivering at the bedside. Therapy for shivering should ideally stop or suppress the central thermoregulatory reflex rather than just uncoupling this response from skeletal muscle contraction, as the latter approach does not mitigate the ongoing cerebral and systemic stress response. Analgo-sedation with opioids, α_2-receptor agonists, or propofol is almost always effective as a last resort to prevent shivering. However, nonpharmacological strategies as first-line interventions for shivering minimize the risk of excessive sedation, which can make neurological examination difficult and increase the risk of complications. The Columbia Anti Shivering protocol has been developed with these strategies in mind, and we base our approach on prospectively collected cooling data on 213 patients who underwent 1,388 patient-days of temperature modulation. Eighty-nine patients underwent hypothermia and 124 patients underwent induced normothermia. In 18% of patients and 33% of the total patient-days, only none-sedating baseline interventions were needed. The first agent used was most commonly dexmeditomidine half the time, followed by opiates and increased doses of propofol. Younger patients, men, and lower body surface area were factors associated with increased number of anti-shivering interventions. As noted by this protocol, a significant proportion of patients undergoing temperature modulation can be effectively treated for shivering without oversedation and paralysis. Patients at higher risk for needing more interventions are younger men with decreased body surface area.

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A10

Controlled prophylactic normothermia

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Critical Care 2012, **16(Suppl 2):**A10

Introduction: Fever is a very frequent complication of intensive care treatment and an independent predictor of unfavourable outcome and mortality in most patients with an acute severe neurologic injury. Today not only treatment but even more prevention of fever has become the focus of intensivists.

Preliminary animal data for the beneficial neuroprotective effect of therapeutic hypothermia could not satisfyingly be reproduced in patients raising questions about the possible side effects of hypothermia. Controlled prophylactic normothermia (36.5°C) prevents secondary injury through consequent treatment of fever and limits dose-dependent side effects through therapeutic hypothermia. Novel endovascular and gel-pad surface cooling measures have shown to be feasible and efficacious in inducing and maintaining even long-term controlled normothermia.

Rationale for treatment of fever: Fever is one of the most frequent complications of intensive care treatment. Up to 90% of patients develop at least one febrile episode within 7 days after being admitted to an ICU [1]. First of all, fever has always to be interpreted as a sign of an infection. Thus temperature modulation by any means has to include a strict protocol identifying any source of infection followed by a straightforward treatment approach. There is widespread consensus that fever alone is associated with unfavourable outcome. This consensus is a result of animal and human data over the past decades. In a meta-analysis conducted by Greer and colleagues including more than 14,000 patients, fever alone was a significant and independent predictor of morbidity and mortality across such different diseases entities as ischaemic stroke, haemorrhagic stroke and traumatic brain injury [2]. Increasing evidence from animal and human studies suggests that fever, irrespective of its cause, can directly and adversely affect neurological outcome in various types of neurological injury [3].

The pathophysiological mechanisms by which fever affects patient outcome are discussed, controversially comprising increase of metabolic demand (under circumstances of reduced supply), production of free radicals, local thermopooling, disruption of the blood-brain barrier, intracranial pressure (ICP) elevation, increased enzymatic inhibition of protein kinases, and worsened cytoskeletal proteolysis [1,3].

Concept of controlled prophylactic normothermia: The aggressive treatment of fever in any patient with a severe acute neurologic injury has become increasingly important and is now the focus of many prospective studies including such patients. Whether the reduction of hyperthermia alone or even controlled hypothermia should be the treatment goal is still

under debate and there are pros and cons for either approach. The enthusiastic preliminary results from animal hypothermia studies could not be satisfyingly reproduced when implemented in human controlled trials, shifting the focus on the possible side effects of hypothermia. Today there is a whole body of evidence that the potentially neuroprotective effects of hypothermia can be significantly diminished by its inherent side effects. It could be shown that hypothermia may lead to increased rate of infections, hypotension, shivering, disturbances in blood clotting, rewarming injuries and significant changes in pharmacokinetics and pharmacodynamics possibly limiting outcome effects of the treated patients [4-8]. Aggressive treatment of fever in the ICU without risk elevation through the side effects of therapeutic hypothermia led to the concept of controlled prophylactic normothermia. This concept is based upon strict control of body core temperature with a target of 36.5°C beginning as early as possible with the goal of complete fever prevention. Prophylactic controlled normothermia can therefore not be compared with the normothermia control group of most randomised trials since this novel approach aims to control temperature prophylactically and is therefore not only treatment of fever.

Experiences from clinical trials: Controlled prophylactic normothermia cannot be achieved through conventional temperature control measures including NSAIDS and conventional cooling blankets [5,9]. In a controlled trial conducted by our study group, reduction of fever burden (that is, body core temperature >37.9°C) was significantly higher in the endovascular cooling group than in the control group although strictly following a predefined fever management protocol including NSAIDS, opioids and conventional cooling blankets in patients with severe cerebrovascular diseases [5]. In this trial an endovascular cooling catheter was placed in the subclavian vein and prophylactic normothermia was maintained over 168 hours in patients with ischaemic stroke and intracerebral haemorrhage and over 336 hours in patients with spontaneous subarachnoid haemorrhage[5]. Safety evaluation revealed no relevant increase in direct device-related adverse events in the endovascular group.

Although there was significant decrease of the fever burden in the device group no difference could be found in the long-term, 6-month, patient follow-up. This lack of outcome efficacy may be attributed due to the increased rate of infectious complications in the device group again pointing out that state-of-the-art temperature modulation has to be combined with a standardised surveillance of infections [6].

In patients with severe traumatic brain injury (GCS ≤8) direct measurement of brain temperature together with ICP is possible [10]. Since fever may deteriorate elevated ICP, prophylactic controlled normothermia should be evaluated in this patient population. In a small pilot trial, brain temperature under endovascular cooling showed that even under normothermia (36.5°C) brain temperature almost reaches body core temperature [11]. This is of utmost interest as brain temperature exceeds body core temperature even under physiological circumstances and even more under fever with a peak gap >2°C [10]. As the brain is the target tissue of all neuroprotectants, it is now evident that even controlled endovascular normothermia can significantly lower brain temperature in TBI patients.

Others could achieve normothermia through a novel surface cooling device using gel-coated energy transfer pads, directly applied to the skin in patients with spontaneous subarachnoid haemorrhage and severe traumatic brain injury [9,12].

Questions to be addressed in future trials: What is the optimal target temperature and duration for temperature modulation in various disease entities? What is the appropriate approach to inherent complications such as shivering, infections, pharmacodynamic and pharmacokinetic disturbances? Are surface and endovascular treatment approaches equivalent?

Conclusion: Controlled prophylactic normothermia is not only fever reduction but aims to strictly maintain the body temperature at 36.5°C. Induced as early as possible the duration should cover the acute phase of the neurological injury, minimising secondary additional neurological impairment though prevention of fever. Endovascular and surface cooling measures using gel-coated pads have shown to be efficacious and feasible in inducing and maintaining normothermia whereas conventional temperature control measures including NSAIDs and conventional cooling blankets are not sufficient to prevent fever. Side effects known from therapeutic hypothermia such as shivering and increased rate of infections also may occur under controlled prophylactic normothermia, although to a lesser extent. Nevertheless, a consequent prevention of those limiting factors should be kept in mind when applying controlled prophylactic normothermia.

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COOLING IN NEUROLOGY AND NEUROSURGERY

A11

Therapeutic hypothermia in traumatic brain injury

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Critical Care 2012, **16(Suppl 2):**A11

Hypothermia has profound effects on the brain function but importantly is potentially protective against both focal and global injuries. Aspects of the biochemical response to acute ischaemia and trauma, which are associated with poor outcome, can be inhibited by cooling. Unlike many pharmacological treatments that tend to antagonise a single neurochemical process, hypothermia offers a simple method of inhibiting multiple pathological processes simultaneously. It therefore has the potential, if applied correctly, to improve outcomes after acute brain injuries, where drug trials have so far failed.

The systemic cooling of patients after acute brain injury is an established treatment modality in many neuro-ICUs. It is a strategy for protecting the injured brain that makes intuitive sense and can reduce both intracranial pressure and the potential for ischaemic secondary insults. Basic science evidence also suggests that cooling can attenuate many secondary biochemical cascades that are activated after acute injury.

However, despite these multiple lines of supportive evidence there is as yet no confirmation from a high-quality randomised controlled trial that prophylactic hypothermia improves outcome or reduces mortality.

This talk will look at the potentially beneficial effects of hypothermia on the biochemistry of acute brain injury, consider the reasons for the failure to demonstrate clinical efficacy and review the supportive data from

meta-analysis, suggesting how hypothermia might be best delivered. Finally I will discuss EuroTherm3235, a European Society of Intensive Care Medicine funded multicentre randomised controlled trial investigating prophylactic hypothermia in traumatic brain injury, which draws on the lessons from the available literature.

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A12

Hypothermia in spinal cord injury

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Historical considerations: In 1862 Edwin Smith, Egyptologist, acquired a papyrus that was thought to be between 2,500 and 3,000 years old. It was translated in 1930 by James Breasted, and was found to contain information on medical therapies performed on 48 patients, including six cases of cervical spine trauma. In the papyrus these injuries were described as 'dislocation of the vertebrae of the neck with unconscious arms and legs, where urine was drained and the phallus was erect, and it was determined that this cannot be treated' [1].

Other physicians like Hippocrates and Claudius Galen made historical reference to the management of spinal cord injury. Galen studied injuries in gladiators, and described 'that injury of the spinal cord caused paralysis and loss of sensation below the level of injury ... and determined that high spinal cord injuries are incompatible with life' [2,3].

Chaulic Guy (1300 to 1360) carried out innovations in the management of traumatic bone injuries by introducing boards and suspensions to treat these fractures; however, he gave a pessimistic view on spinal injuries [4,5].

Ambrose Pare (1510 to 1590) developed spine surgery, and along with Hildanus Fabricius (1560 to 1634) used traction techniques, reduction and utilization of wood frames to treat cervical spine fractures [6].

Louis Pasteur's (1822 to 1895) surgical innovations and discoveries and the advent of asepsis and antisepsis by Semmelweis (1816 to 1868) and others, and primarily the application of general anesthesia by Morton (1819 to 1868) and others gave a new impulse to this field. Together these developments helped reduce surgical mortality and infections [5,7].

In the nineteenth century, anatomy and physiology of the central nervous system were studied. The neuron doctrine was developed by Santiago Ramon y Cajal (1852 to 1934), who demonstrated the individuality of nerve cells and the connections that they have with each other [8,9].

Alfred R Allen between 1908 and 1911 developed a reproducible and quantifiable model that allowed induction of a uniform traumatic injury to the spine, and also explained the pathophysiological changes seen in spinal trauma, including key aspects of secondary spinal cord injury. In 1972 Tarlov showed that symptoms caused by compression of the spinal cord for more than 12 hours could sometimes still be reversed. During this period 'progressive central hemorrhagic necrosis' was identified, which consists of bleeding from the gray matter of the spinal cord central necrosis and destruction of white matter, with subsequent cavitations [10,11]. Finally, one of the possible immunomodalities of neuroprotection was suggested in 1968 by Albin and White who applied local hypothermia with favorable results in animals [12]. However, use of hypothermia was limited due to fear of side effects [13-17].

These preliminary studies were difficult to interpret due to the limited number of patients, lack of controls, concomitant surgical procedures and the concomitant use of drugs such as methylprednisolone [18]. In recent years there has been a renewed interest in the use of moderate therapeutic hypothermia due to its demonstrated neuroprotective effects in other areas. In Panama, we have been administering therapeutic hypothermia in selected cases with severe spinal cord injury. More frequently we apply fever management through endovascular, surface pads or medical thermomodulation protocols.

Epidemiological aspects of spinal cord injury: No accurate numbers on spinal cord injury are available for Panama and Central America. In the United States there are around 12,000 new cases of traumatic spinal cord injury each year, not including those who die at the scene of the accident [19]. Approximately 1.3 million Americans have some type of chronic paralysis resulting from spinal cord injury [20,21]. The leading causes are motor vehicle accidents (41.3%), falls (27.3%), acts of violence (15%) and recreational activities (7.9%). Apart from the medical and personal consequences for the patient, the economic impact in terms of ability to work is significant.

Spinal cord injury, neurophysiological aspects - how can therapeutic hypothermia help?: We will provide a concise description of the pathophysiological changes that occur after a spinal injury that might justify use of therapeutic hypothermia to mitigate ongoing destructive processes.

Spinal cord injury is a process that can be divided into three phases [22,23]. The *primary mechanism* refers to the direct mechanical damage. This may include compression, stretching, persistent concussion, contusion, compression and laceration of the spinal cord [22,23]. The *secondary mechanism* involves a cascade of events at the cellular level triggered by the primary mechanism. These biochemical events are responsible for increased tissue damage and promote the apoptotic cascade. These include those listed in Table 1. The *healing mechanism* (third mechanism) begins in the days after injury and can last for months or years. This can paradoxically increase the neurological damage. Healing in the primary injury takes place by neutrophils, macrophages and lymphocytes, reactive astrocytes, Schwann cells, meningeal fibroblasts, and microglia invasion. Scar formation forms a barrier for cellular and molecular axonal regeneration.

Therapeutic hypothermia has been used in various types of neurological injury such as stroke, post-anoxic encephalopathy, and traumatic brain injury. Some of these results have been extrapolated to spinal cord trauma patients.

Moderate therapeutic hypothermia has been shown to affect the apoptotic cascade as well as other destructive mechanisms, ranging from improved energy balance, reduction of mitochondrial dysfunction, decreased vascular permeability and capillary leakage, mitigation of cell membrane injury, improvement of intracellular acidosis, mitigation of DNA injury, reduction in metabolic demand, and a decrease in proinflammatory cytokine and free radical release [24-28].

It is important to realize that there is a window time, perhaps several hours to days after the injury, during which this treatment modality can influence the course of events [29].

Experimental studies and supporting evidence: Yu and colleagues used therapeutic hypothermia (33°C) after 30 minutes of ischemic injury to the thoracic spinal cord in rats, and reported improvement of motor function at the microscopic level associated with cooling [30]. Others reported improvements in functional outcome in various animal models associated with cooling [30-32]. In an animal study of spinal cord ischemia, hypothermia increased the duration of ischemia required to produce neurological deficits [31].

Moderate hypothermia has also shown potential benefits in invasive procedures including aortic clamp cross-clamping during thoracic surgery [33,34]. This can be regarded as indirect evidence that hypothermia could protect the spinal cord from ischemic injury, although the mechanisms in traumatic injury may be different from surgical trauma and ischemia.

Fever is a common complication in patients with spinal cord injury [35-37]. Of the identifiable etiologies the most common cause is infection (especially pneumonia and urinary tract infections). However, fever of unknown origin is the most frequent diagnosis, occurring in 66% of patients. It should be realized that patients with spinal cord injury have a high incidence of thermoregulatory problems, which can contribute to the high incidence of FUO [38,39].

Of note, Yu and colleagues demonstrated in an experimental study in rats that post-traumatic hyperthermia in thoracic spinal cord injury worsened behavioral and histopathological damage compared with normothermia, and was associated with an increase of overall contusion volume by increasing the vulnerability of both gray and white matter structures compared with normothermia [40].

Role of moderate hypothermia in the clinical scenario of patients with spinal cord injury: Early clinical studies with irrigation to induce

Table 1(Abstract A12)

1. After the death of an oligodendrocyte, a progressive Walerian degeneration takes place from the site of primary injury, compromising the integrity of axons and mitochondria. Simultaneously caspase activation and apoptosis occur, leading finally to demyelination and release of nerve growth factor.
2. Vascular ischemia, impaired autoregulation, neurogenic shock, radial and axial hemorrhage, compromised microcirculation, collapsed veins, venous obstruction, vasospasm and thrombosis.
3. Ionic alterations: intracellular and extracellular calcium overload, increase of sodium and potassium.
4. Accumulation of neurotransmitters such as dopamine, norepinephrine, serotonin and glutamate at the extracellular level.
5. Release of arachidonic acid, production of free radicals and lipid eicosanoid peroxidation.
6. Endogenous opioid activation
7. Formation of cytotoxic and vasogenic edema
8. (Hyper)inflammatory response
9. Failure of ATP-dependent intracellular processes

local hypothermia produced conflicting results [41]. However, the advent of more reliable cooling devices that can better maintain body temperature within a predetermined range have improved our ability to deliver targeted therapy.

Hypothermia has been used to protect the spinal cord and prevent paraplegia during high aortic cross surgery. In one study with long-term follow-up, the incidence of spinal cord injury in patients undergoing high-risk thoracoabdominal aneurysm repair under hypothermia over a 10-year period the risk of SCI was 18% in hypothermic patients compared with 29% in historical controls (P <0.01) [29,33].

Interest in hypothermia for spinal cord injury received a boost when in 2007 a high-profile case was reported. An NFL player suffered a complete AIS A cervical spine injury, and was treated immediately on the football field with moderate hypothermia. This individual had a much better than expected outcome and this led to a spate of publications on the potential use of hypothermia for spinal cord injury [40,42-44]. Of course, such anecdotal evidence cannot prove the benefit of any therapy, and professional organizations such as the American Association of neurological surgeons, Neurological and Spine Surgery Joint Sections and Joint Section of Trauma concluded that there was currently not enough evidence available to recommend or discourage the practice of therapeutic hypothermia as a treatment for spinal cord injury [42,45-47].

In 2009 Levi and colleagues successfully tested the safety and feasibility of systemic hypothermia induction in spinal cord injury with an endovascular cooling device [48]. The authors treated 14 patients with AIS A spinal cord injury with moderate hypothermia. At a median follow-up of 1 year they found an improved conversion rate: in 6/14 cooled patients there was an improvement of the neurological examination (three patients improved to AIS B, two patients improved to AIS C and one patient improved to AIS D). This represents an improvement rate of 42.8%, higher than the 12.5 to 20% found in various other studies where patients had not been treated with hypothermia [49,50]. Complications associated with cooling were mostly respiratory issues (atelectasis and pneumonia) but these rates were similar in the other studies where cooling had not been used. Adverse events such as coagulopathy, deep venous thrombosis and pulmonary embolism were not reported in the patients treated with hypothermia. This is the first investigation on the safety systemic cooling in acute spinal cord injury [48,51]. To determine efficacy will require randomized controlled clinical studies. Currently there are plans to organize such a trial, which will involve 17 centers to determine whether moderate hypothermia improves outcome in a larger population of patients with acute spinal cord injury. Details can be found at online: http://www.miamiproject.org. The protocol calls for induction of hypothermia within 6 hours of injury, to be maintained by endovascular cooling, where they will evaluate the safety of different durations of hypothermia, outcomes and risks [47].

Fever in patients with spinal cord injury, if not controlled promptly, may lead to increased morbidity and mortality because of hyperthermic damage to cells. Therefore controlling fever is an important goal of care in these patients. Preliminary data suggest that endovascular cooling can be used effectively for this purpose [52,53].

There are no proven treatments with high grades of scientific evidence for the devastating consequences of spinal cord injury. In Panama, selected patients with ASIA A lesions are treated with therapeutic cooling for a period of 24 to 48 hours. This can be done in either mechanically ventilated or nonventilated patients. Other aspects of treatment include keeping adequate medullar perfusion pressure, normothermia throughout their ICU stay (accomplished by pharmacological interventions, mechanical cooling either with a surface cooling or endovascular device), early enteral immunonutrition, and various tests such as somatosensory evoked potentials.

Conclusion: So far there are no proven therapeutic interventions that improve outcome in severe spinal cord injury. Hypothermia appears to be a promising treatment in this population, and needs to be studied in prospective clinical trials. Fever control should be a goal of care in these patients.

Acknowledgements: The author thanks Dr Kees Polderman, Dr Guillermo Castillo, Dr Waltter Kravcio, Dr Javier Alvarado and Franklin Paulino for their support.

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A13

Phase 2/3 study of intravenous thrombolysis and hypothermia for acute treatment of ischemic stroke (ICTuS 2/3)

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Critical Care 2012, **16(Suppl 2):**A13

Background: The ICTuS trial showed feasibility of endovascular hypothermia for acute ischemic stroke [1]; ICTuS L confirmed safety and feasibility of endovascular hypothermia during thrombolysis [2]. The ICTuS 2/3 study seeks to determine whether the combination of thrombolysis and hypothermia is superior to thrombolysis alone for the treatment of acute ischemic stroke. A phase 2 study will include 450 patients to assess the safety of various protocol changes, to demonstrate sufficient recruitment, and to allow an interim analysis for futility. If pre-specified milestones are achieved the study will be enlarged to a 1,800-patient phase 3 efficacy study.
Methods: This is a prospective, randomized, single-blind, multicenter phase 2/3 study. We aim to include ischemic stroke patients treated within 3 hours of symptom onset with IV tPA (according to FDA or EMEA protocol), NIHSS ≥7 and ≤20, age 22 to 80. Patients are randomly assigned to either hypothermia permissively targeted to 33°C or normothermia. Favorable outcome is defined as a 90-day Modified Rankin score (mRS) of 0 or 1. Secondary outcome measures are: 90-day NIHSS, Barthel Index (BI), mortality, shift analysis of the mRS, global odds ratio of mRS, BI, NIHSS, incidence of symptomatic intracranial hemorrhage and 90-day Montreal Cognitive Assessment. An interim analysis for futility is planned near the end of phase 2. In addition to futility, analyses will assess the frequency of target temperature reached within 6 hours from symptom, pneumonia rate, safety profile of iced saline infusion and study-wide average enrollment rate.
Results: The study team initiated 11 study sites in the USA and two in Europe. Enrolment began in December 2010. Currently, 37 subjects are

enrolled. A full DSMB review of experience to date allowed the study to continue enrollment. A safety review after the first 50 patients is expected in late 2012.

Conclusions: ICTuS 2/3 is the largest trial of endovascular hypothermia for acute stroke currently running. There appear to be no safety or feasibility concerns.

Acknowledgements: NINDS grants P50NS5044148 (UCSD) and P50NS044227 (Houston).

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A14

Therapeutic hypothermia decreases growth of perihemorrhagic edema and prevents critical increase of intracranial pressure in large intracerebral haemorrhage

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Critical Care 2012, **16(Suppl 2):**A14

Background: Intracerebral hemorrhage (ICH) accounts up to 15% of all first-ever strokes and is associated with high mortality, morbidity, and disability [1,2]. Main factors contributing to poor outcome within the first days after symptom onset are hematoma size, early hematoma growth, the presence of intraventricular hemorrhage, and the size of perihemorrhagic edema (PHE) [3]. PHE leads to secondary injury by a complex pathophysiological cascade following ICH. Above all, mass effects of PHE can lead to critical increase of intracranial pressure and subsequent herniation. Since the volume of PHE increases within the first days after ICH and is correlated to ICH volume, PHE represents a meaningful target for interventions [3]. Therapeutic hypothermia (TH) is a promising candidate to treat or even prevent PHE. Experimental data indicate that TH is neuroprotective after acute brain injury including ICH and reduces PHE [4]. In a proof of concept study, we investigated the effects of mild TH of 35°C over a period of 10 days in patients suffering from large (>25 ml) ICH and compared these patients with a historical control group [5]. Even with standard treatment, ICH of this size has an extremely high mortality and almost never leads to acceptable neurological outcome [2]. In our study, TH prevented the increase of PHE and led to a superb in-hospital survival rate and an acceptable long-term survival and grade of neurological deficits [5,6]. Because of these promising results, we established an institutional protocol in the Department of Neurology at University Hospital Erlangen and treated patients with large ICH with mild TH. Here, we report data of 20 patients with large ICH treated in our neuro-ICU.

Materials and methods: All patients with large ICH were treated by a detailed institutional protocol that is in line with our ongoing prospective study [7]. Patients aged over 18 years with primary ICH at the level of the basal ganglia or thalamus and a hematoma volume of over 25 ml on initial CCT were treated by TH. Patients have been treated within the first 12 hours after symptom onset if they had a score on the Glasgow Coma Scale (GCS) of ≤8 at presentation or early worsening by 2 points with subsequent endotracheal intubation and neurointensive care treatment. All patients received invasive ICP measurement by external ventricular drainage or a parenchymal probe. Relatives were informed about the treatment and approved this regimen. Patients have not been treated by TH if any clinical signs of herniation such as pupillomotoric defects or bilateral signs of the pyramidal tract at baseline could be observed or the treating team agreed to a do-not-resuscitate order. Laboratory exclusion criteria included an international normalized ratio >1.5, a thrombocyte count below 70,000/µl or leukocytosis >20,000/µl on admission. The presence of intraventricular hemorrhage has not been an exclusion criterion, since we have a standardized protocol, including external ventricular drainage, intraventricular clot lysis and the use of lumbar drainage. Patients who have been randomized to the control arm of our multicenter randomized controlled trial CINCH [7] are not reported here.

Intervention of therapeutic hypothermia: Patients were treated with an endovascular catheter-based cooling system (ICY catheter; Zoll Medical, USA) positioned in the femoral vein as described previously [5]. The target temperature has been set to 35.0°C. The body core temperature has been measured by a urinary bladder catheter. As soon as body core temperature drops below 36.0°C, patients are covered by a warming blanket to avoid shivering. Ten days after initiation of TH, patients received slowly, controlled rewarming by 0.1°C/hour. The catheter has been changed at least once during the treatment period, preferably on day 4 ± 0.5 after ICH, or if clinically indicated

Outcome analysis: Patients have been analysed for in-hospital mortality, mortality and functional outcome (modified Ranking Scale and Barthel Index) on days 90 and 180 after ICH.

Semiautomatic assessment of ICH and PHE volume: The Siemens Leonardo V software for semiautomatic CT volumetry has been used for assessment of hematoma and perihemorrhagic edema volumes. The procedure has been described in detail before [3].

Statistical analysis: Statistical tests were performed with SPSS 16.0 software package. Data are given as mean ± standard deviation, if not indicated differently. Normality of distribution was tested using the Shapiro-Wilk and Kolmogorov-Smirnov tests. Absolute edema values were not distributed normally. Accordingly, single comparisons of absolute edema between the two groups at different time points were performed using the nonparametric Mann-Whitney *U* test. All other data were distributed normally. The unpaired *t* test was used for single comparisons of ICH values between the two groups. $P < 0.05$ was considered significant.

Results: Patient characteristics: A total of 20 patients have been treated with mild hypothermia so far. There have been no significant differences between these patients and our historic control group ($n = 25$; Table 1). Overall, the volume of ICH in the initial CT was large with 57 ± 25 ml for the hypothermia group and 59 ± 31 ml for the control group. The mean volume of PHE after ICH has been calculated from cranial CT. Day 1 indicates the CT before start of hypothermia or standard treatment. Rewarming was started at day 10. A significant difference ($P < 0.05$) of the volumes at the specific day between the control and hypothermia group was found [5].

Volume of PHE assessed in CT: While there was no significant difference between the PHE on days 1 and 2, we found significantly higher volumes of PHE in the historic control group on days 3, 6, 11, and 14. Importantly, PHE did not increase after rewarming at days 11 and 14.

Complications of therapeutic hypothermia: ICP crisis: none of the patients in the hypothermia group had ICP crisis, in contrast to 11 (44%) patients in the control group.

We detected deep venous thrombosis in one patient in the hypothermia group. Shivering appeared in nine (45%) patients and was treated sufficiently by medication including meperidine and, if needed, muscle relaxants. Pneumonia was the most common complication in hypothermia patients. Nineteen (95%) of the patients developed pneumonia, three suffered from ARDS and sepsis. In contrast, pneumonia appeared in 79% of the control patients. Two (10%) patients in the hypothermia group had a ventriculitis during external ventricular drainage. Five (25%) of the hypothermia patients showed a decrease of thrombocytes. However, the thrombocyte count never dropped below 80,000/µl and no complications associated to this decrease could be detected. Four patients (20%) developed bradycardia of below 40 beats per minute, but only one patient received treatment due to bradycardia. One patient (5%) had a pulmonary embolism during hypothermia. However, we could not detect deep venous thrombosis or any other source for PE.

Clinical outcome: Eighteen patients survived the first 90 days after ICH. Two showed a mRS of 3, seven had a mRS of 4, and eight a mRS of 5 after 90 days. Follow-up assessment after 1a showed that 17 patients survived ICH. Of the surviving patients, 10 patients had a mRS of 3, 12 had a mRS of 4, and two had a mRS of 5.

Discussion: PHE develops early after ICH, causes an additional mass effect after ICH, and contributes to secondary brain injury [3,4]. This mass effect can be critical especially in large ICH and leads frequently to ICP crisis and brain herniation [3,5,6]. Therefore, PHE is an important target for therapeutic interventions. Animal experiments and clinical data show that TH is a promising candidate for edema and ICP control [4-6]. We could show in a previously published case series that TH decreased PHE and led

Table 1(Abstract A14) Patient characteristics (from [5])

	Therapeutic hypothermia (*n* = 20)	Historic control (*n* = 25)
Age (years)	62 ± 9	67 ± 7
GCS	5 (3 to 10)	8 (3 to 10)
ICH volume on admission (ml)	57 ± 25	59 ± 31
PHE on admission (ml)	49 ± 40	40 ± 28
Number of patients with intraventricular hemorrhage	13	14

ICH, intracerebral hemorrhage; PHE, perihemorrhagic edema.

to acceptable short-term and long-term survival [5,6]. Therefore, we implicated a TH as the standard care for large ICH in our institution and we initiated a German-Austrian controlled multicenter trial to overcome the shortcomings of our historical control group [7].

Here, we report results of the routine use of prolonged mild therapeutic hypothermia in patients suffering from large ICH at the level of the basal ganglia or thalamus. TH prevented the increase of PHE, prevented ICP crisis and lead to an acceptable long-term outcome compared with the historical control group. Importantly, rewarming did not lead to rebound edema as measured by CT. However, TH was also associated with complications, of which infections were the most frequent ones. As this study underscores the promising results of our proof-of-concept study, we are looking forward to the results of the CINCH study and other clinical data investigating the effects of temperature and temperature management of PHE in large ICH.

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COOLING IN INTENSIVE CARE AND INTRAOPERATIVE MANAGEMENT

A15

Hypothermia in burns intensive care: use of the intravenous temperature management system Thermogard XP®

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Critical Care 2012, **16(Suppl 2):**A15

Introduction: The care of the patient with major burns in the ICU is a complex and challenging task. They differ from the other critical care patient groups in several ways. One of the major challenges faced is confronting their hypermetabolic state and temperature management [1].

It is widely known that major burn injury is associated with the most profound of hypermetabolic responses to a pathological state. Hyperthermia that is non-infectious is a feature of the systemic inflammatory response to this. In burns intensive care, the disproportionate increase in metabolic rate to small rises in core temperature can have significant impact on resuscitation and prognosis. The pathophysiology of the hyperthermic response in major burn injury is poorly understood. It could be secondary to an infective etiology or a metabolic response to the systemic inflammation. Irrespective of the reason, sustained hyperthermia above 40°C can culminate in cellular injury and death [2].

The hypermetabolic response starts within the first 5 days of the major burn and can last for a year after the injury. Because of the ongoing systemic inflammatory stimulation, patients with major burns often have pyrexia and their thermoregulatory system reset at a higher baseline temperature around 38.5°C [3].

While therapeutic cooling is widely used in neuro intensive care in the management of hyperthermic brain-injured patients and in patients after out-of-hospital cardiac arrests, there is very scarce literature available on the management of hyperthermia in burns intensive care. We, in this article, would like to share our experience of using the intravascular temperature management system (IVTM) Thermoguard XP® in our unit to manage refractory hyperthermia in patients with major burns. We report the responses of two major burns patients to core intravascular thermoregulation during periods of severe hyperthermia (>40°C).

Case 1: A 24-year-old male had sustained 80% mixed depth, total body surface area (TBSA) flame burns following a road traffic accident. He had no significant past medical history. Initial resuscitation including endotracheal intubation and fluid resuscitation was instituted in the nearby district general hospital and was transferred over to our burns ICU without much delay. On admission to the ICU, detailed assessment of the burn injuries revealed second-degree and third-degree burns involving the trunk, abdomen, back, upper and lower extremities. Initial temperature recorded was 34°C. He responded to external warming, which included nursing in a warm environment, use of warm air blanket and warm fluids.

The patient underwent extensive escharatomies on the day of admission as a part of his initial resuscitation. He developed multiorgan failure requiring high inotropic support, renal replacement therapy and high FiO_2. He developed hyperpyrexia (temperature >42°C) on day 11 post burn.

Relevant microbiology investigations had demonstrated no obvious focus of ongoing infection. The hyperpyrexia was resistant to conventional active cooling (bladder/gastric lavage, hemofiltration, external cooling with cooling blanket). The hyperpyrexia was associated with marked tachycardia (heart rate >150 beats/minute) with increasing oxygen demands and hypotension with escalating inotropic support. Forced core thermoregulation was commenced due to instability attributed to high core temperature.

The Thermogard XP® was inserted in the femoral vein, the target temperature was set at 37°C. Within 2 hours of initiating the IVTM, the core body temperature dropped by 3°c down to 39°C. It took a further 3 hours to stabilise at the target temperature of 37°C.

The IVTM system was used for a period of 6 days. The objective measurements of pulse rate, blood pressure, respiratory rate and urine output were seen to improve in the presence of a normothermic state (Figure 1). After a protracted and convoluted stay in the ICU, the patient was discharged to a ward after 38 days.

Case 2: A 34-year-old female, a known intravenous drug abuser, admitted to burns ICU following an attempt of deliberate self-harm. The patient, heavily drunk, allegedly grasped a high-voltage (400 kV) live wire on a pylon and was found 15 feet away; she had sustained polytrauma

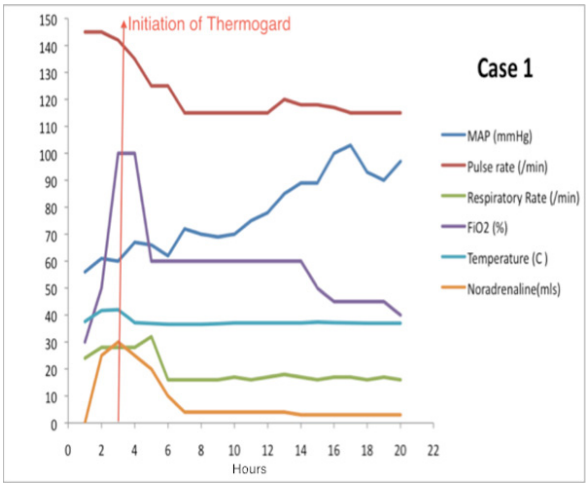

Figure 1(abstract A15) Response in vital parameters in the first 20 hours after initiating IVTM: case 1.

requiring splenectomy for splenic rupture and chest drains for pneumothoraces. She had suffered deep thermal burns involving 27% TBSA.

She had escharotomies on her both upper extremities and chest within hours of admission. Patient subsequently developed rhabdomyolysis, myoglobinuria and renal failure. The patient remained ventilated, requiring ionotropic support and haemofiltration. She remained hyperpyrexial from day 1 post burn; however, the temperature crept above 41°C on day 5 post burn. The temperature was persistently high despite appropriate broad-spectrum antibiotics, antifungal therapy and conventional methods of cooling. Physiological instability led to the addition of forced core thermoregulation on day 8. The target temperature of 37.5°C was achieved over a period of 4 to 8 hours with resultant improvement in pulse and respiratory rates and reduced inotrope levels (Figure 2). The forced core thermoregulation was held periodically to assess the relapse of hyperthermia and was reinstated as required.

Discussion: Thermoregulatory failure leading to elevation of core body temperature more than 37.5°C (37.5 to 38.3°C) is hyperthermia. The core body temperature is managed in a tight range by the balance of heat production and heat loss.

The detrimental effects of hyperthermia on a patient in intensive care cannot be overstated. Hyperthermia in adults with major burns is not uncommon; however, the extent of the problem is not known. From other cohorts like patients with brain injury, it is well known that hyperthermia is an independent predictor of increased length of stay and poor outcome in the ICU [4]. The impact of hyperthermia on various organ systems and mortality depends on the degree of temperature elevation and rapidity of cooling to normal temperatures.

Among the various methods to instigate therapeutic cooling in intensive care, conventional methods could lead to treatment failure in as high as 60% of patients and the IVTM system is deemed most reliable to maintain a stable temperature [5].

Forced core thermoregulation using the IVTM system is effective in regulating labile body temperatures associated with severe burns [6]. The thermoregulation is achieved by circulation of saline via a ballooned catheter inserted into the central venous system, with automatic adjustment of saline temperature controlled by remote monitoring of patient temperature.

The downsides of using IVTM systems are the need for a central venous access and complications related to it, cost factor and also use of thermoregulatory systems may mask underlying physiological changes, potentially leading to delayed or mismanagement of any precipitants of hypothermia or hyperthermia, for example sepsis. Documentation of an artificially maintained temperature on an observation chart without reference to Thermogard XP® activity has implications for both immediate patient management and retrospective review of observation charts for audit or medico-legal purposes. Currently, facilities to download data directly from the Thermogard XP® electronic system are cumbersome and not readily available in most ward settings. We devised and used a qualitative method of documenting Thermoguard XP® activity. Firstly, a 'T' on the observation chart to denote the presence of a Thermogard XP® *in situ*. Secondly, a number assigned from a scale of +4 to -10 to represent the extent of warming or cooling, correlating with the bars displayed on the Thermogard XP® screen. These two pieces of information were documented alongside the patient's core temperature every time observations are performed. We, in addition, developed an adhesive label that replicates the cooling/warming scale displayed on the Thermogard XP® screen, allowing an arrow to be documented on the chart as depicted on the

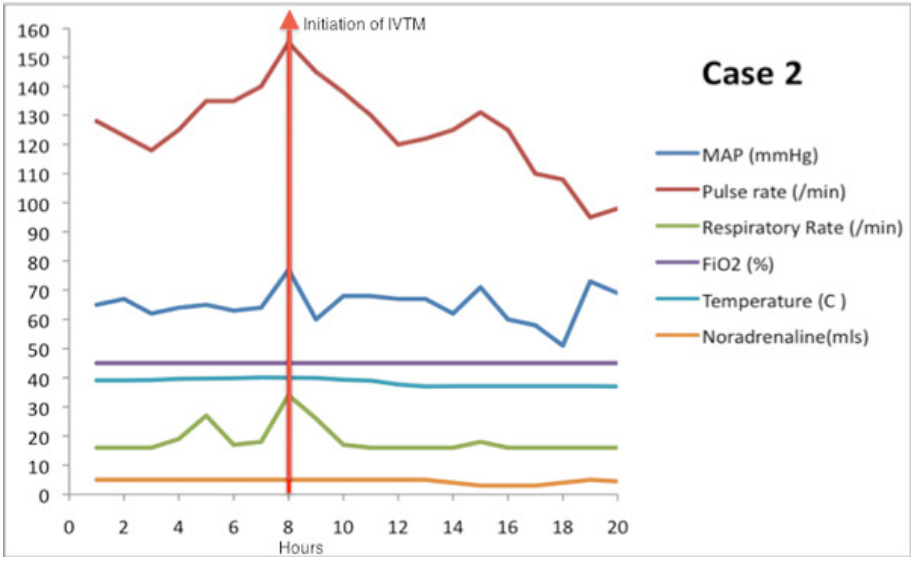

Figure 2(abstract A15) Response in vital parameters in the first 20 hours after initiating IVTM: case 2.

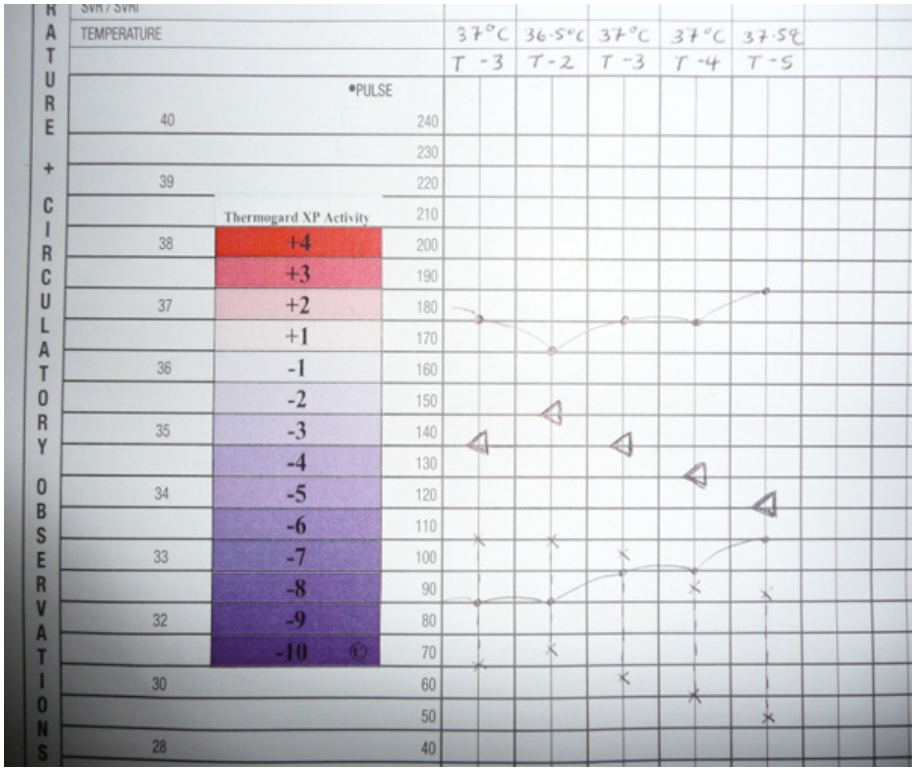

Figure 3(abstract A15) Adhesive label that replicates the cooling/warming scale displayed on the Thermogard XP® screen, allowing an arrow to be documented on the chart.

screen (Figure 3.) It provided a more visual representation of Thermogard XP® activity and was used as an adjunct to the above numerical scale. All members of the multidisciplinary team could observe our method of documenting trends in core body temperature/ Thermoguard XP® activity at a glance. It is reproducible in any unit caring for critically ill burns patients.

Conclusion: The directed response of hyperthermia in febrile and nonfebrile states has physiological merits when considering the requirements of inflammatory mediators and cells. Forced core thermoregulation has aided us in the early management of unstable intensive care patients with refractory hyperthermia.The use of an IVTM system and subsequent documentation of artificially maintained temperature can be misleading and has implications for patient management and retrospective review.

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A16

Hypothermia after aneurysmal subarachnoid hemorrhage

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Critical Care 2012, **16(Suppl 2):**A16

Introduction: Aneurysmal subarachnoid hemorrhage (SAH) is a common and frequently devastating condition, accounting for 1 to 7% of all strokes with an incidence of 9.1 per 100,000 [1]. Major advances in SAH management over the past three decades have decreased case fatality by 0.8% per year, but it is still 40% and many survivors have long-term disabilities [2]. The most important and potentially treatable complication is development of delayed cerebral ischemia (DCI), which can progress to cerebral infarction associated with poor outcome.

The pathogenesis of DCI is multifactorial and assumed to be initiated in the early phase of SAH [3]. The onset of SAH is characterized by a short-lasting and cerebral perfusion pressure (CPP)-dependent decrease in cerebral blood flow (CBF) leading to global cerebral ischemia [4]. Elevated intracranial pressure (ICP) and acute cerebral ischemia are the main factors for early disruption of the blood-brain barrier as well as impairment of autoregulation associated with brain edema and brain swelling. Important pathogenic mechanisms of CPP-independent hypoperfusion include acute vasoconstriction, cortical spreading ischemia, and activation of the inflammatory response. The release of oxyhemoglobin and endothelin-1 (ET-1) are the key factors for cortical spreading ischemia, reduced nitric oxide (NO) availability, and secondary cytotoxic edema formation. Cerebral vasospasm (CVS) is a delayed morphological narrowing of cerebral arteries, occurring 4 to 10 days after SAH. Although CVS have been associated with DCI, it is generally accepted that CVS is not solely responsible for DCI [5]. In fact, DCI may occur in the absence of CVS and *vice versa* and the distribution of

CVS may fail to reliably predict the subsequent pattern of cerebral infarction [6].

Neuroprotective strategies to prevent DCI have been mainly focused on treatment of CVS, but despite extensive research, effective and/or causative prophylaxis and treatment are not available [7]. So far, oral nimodipine is the only drug that can reduce the incidence of DCI and poor outcome, but there is no beneficial effect on CVS [8]. Hypothermia (HT) treatment exerting numerous protective effects such as a decrease in cerebral metabolism [9], stabilization of the blood-brain barrier [10], reduction of cerebral edema [11], suppression of excitatory neurotransmitter concentrations [12] and inflammatory reactions [13] seems to be well suited as a neuroprotective strategy. In the following, the clinical application of HT after SAH is presented by reviewing the existing literature.

Hypothermia during aneurysm surgery: In the past, promising studies on intraoperative HT during aneurysm surgery as an attempt to reduce ischemic injury have been published [14-18]. The Intraoperative Hypothermia for Aneurysm Surgery Trial (IHAST) applied HT in a randomized study in 1,001 patients with good-grade SAH (WFNS 1 to 3); however, it found no improvement in neurological outcome 3 months after surgery [19]. *Post-hoc* analysis demonstrated no difference in the incidence of cognitive impairment between hypothermic and normothermic groups [20]. Furthermore, there was no evidence for the benefit of intraoperative HT on 24-hour and 3-month outcome in patients who underwent temporary clipping [21]. It has to be noted that these results only apply to good-grade SAH patients and may not be extrapolated to the general SAH population. This suggests that only a carefully selected subgroup of patients, with specific complications induced by SAH, may benefit from HT treatment at a particular time and for certain duration.

Hypothermia in patients with poor-grade subarachnoid hemorrhage: Several experimental studies have demonstrated that HT is effective in minimizing neuronal damage, if induced before or early after the SAH. Kawamura and colleagues found a reduced expression of c-jun and hsp-70 mRNA, indicating a reduced stress response that may otherwise manifest as necrosis or apoptosis [22]. Thome and colleagues and Schubert and colleagues demonstrated that early induction of HT, up to 60 minutes after SAH, reversed CPP-independent hypoperfusion and brain edema formation, preserved cerebral autoregulation, and reduced accumulation of lactate and glutamate [11,12,23]. On the other hand, delayed induction of HT, up to 180 minutes after SAH, failed to reduce brain edema formation, thus indicating a limited time window of HT application [24]. However, HT was effective in reducing ICP and associated with improved neurological recovery. These studies encourage early induction of HT in poor-grade SAH patients, for example, as soon as signs of brain swelling are seen on CT scans.

So far, only few retrospective case series have investigated the effect of mild HT during the acute phase of SAH. Table 1 presents an overview of these studies applying HT within 24 hours after SAH to patients with poor-grade SAH (WFNS 4 to 5). The duration of HT varied between 2 and 14 days. Overall outcome results were unsatisfactory with a mortality rate of 47.4% and favorable outcome in less than one-quarter of cases. Yasui and colleagues evaluated seven patients admitted within 6 hours from symptom onset and treated with HT for 48 hours [25]. PET studies during HT revealed a reduction in cerebral oxygen metabolism exceeding the decrease in CBF, thus indicating a state of luxury perfusion. However, according to the Barthel Index only two patients were independent, one was partially dependent, able to walk without assistance, and more than one-half of the patients bedridden at 12 months after SAH. Anei and colleagues compared outcome results before and after introduction of HT treatment to their institution and found no significant difference in the mortality rate with 56.3% and 57.9%, respectively [26]. The authors noted that post-HT fever can be a serious complication resulting in brain swelling and unfavorable outcome. In contrast to these studies, Gasser and colleagues showed more promising outcome results in 21 patients with poor-grade SAH (WFNS 4 to 5) and induction of HT after developing intracranial hypertension (>15 mmHg) that was refractory to conventional treatment. HT was induced on average 4.2 ± 3.3 days after SAH and maintained for 4.3 ± 3.9 days. Prolonged HT (>72 hours) was associated with an increased risk of systemic complications, but 10 patients (47.6%) showed favorable outcome (GOS 4 to 5) and five patients died (23.8%).

Hypothermia in patients with delayed cerebral ischemia/cerebral vasospasm: Recently, a SAH-CVS model in dogs demonstrated that HT can attenuate the degree of CVS up to 14 days after SAH, possibly by regulating the levels of ET-1 and NO [27]. The duration of HT was directly proportional to the duration of relieving CVS. Table 2 presents an overview of clinical studies applying HT to patients with symptomatic CVS leading to DCI. Nagao and colleagues treated five patients with good-grade SAH (H&H I to III), starting HT either during delayed aneurysm clipping or if CVS was refractory to hyperdynamic and endovascular therapy [28]. Four patients survived with favorable outcome and one patient was severely disabled. In a follow-up study, Nagao and colleagues included eight patients with good-grade SAH (H&H II to III), and seven patients had favorable outcome and one survived severely disabled [29]. According to SPECT studies, HT was associated with decreased CBF levels in all patients. Nakamura and colleagues reported a reduction in arterio-jugular oxygen difference ($AVDO_2$) during HT in five patients (H&H III to IV), thus indicating a reduced metabolic demand [30]. All patients received hyperdynamic therapy before and during HT, but outcome results were unsatisfactory. Possible contributing factors of poor outcome include a higher grade of SAH and it is unclear whether endovascular treatment was applied or not. In our series of 100 SAH patients treated with HT, 28 patients had symptomatic CVS refractory to hypertensive therapy and endovascular treatment [31]. HT was combined with barbiturate coma in 23 of 28 patients and maintained until CVS resolved or severe side effects occurred (mean duration 5.7 ± 3.3 days). Although the majority of patients had poor-grade SAH (H&H 4 to 5 in 57.1%, Fisher 3 to 4 in 85.7%), favorable outcome (GOS 4 to 5) was achieved in 57.1%. In patients with intracranial hypertension (>20 mmHg) with and without refractory CVS, favorable outcome was obtained in only 25.0% and 26.5%, respectively. Systemic side effects possibly caused from HT and/or barbiturate coma included pneumonia in 52.0%, thrombocytopenia (<100,000/μl) in 47.0%, septic shock syndrome in 40.0%, and acute respiratory distress syndrome in 16.0%. In a subgroup of seven patients with combined HT and barbiturate coma, daily levels of IL-6, IL-1β, TNFα, and leukocyte count in the cerebrospinal fluid and plasma were quantified [13]. IL-6 levels in the cerebrospinal fluid and systemic IL-1β levels were significantly lower compared with patients receiving barbiturate coma alone (n = 8), thus indicating HT-related attenuation of the inflammatory response.

Table 1(Abstract A16) Studies applying hypothermia on day of aneurysm rupture to patients with poor-grade SAH (WFNS 4 to 5 or H&H IV to V)

Study	Number of patients (*n*)	Target temperature (°C)	Duration of hypothermia (days)	Favorable outcome*, % (*n*)	Mortality rate, % (*n*)
Nagao and colleagues (2000)	9	32 to 34	5 to 14	44.4% (4)	55.6% (5)
Yasui and colleagues (2002)	7	33 to 34	2	42.8% (3)*	0.0% (0)
Nakamura and colleagues (2002)	3	32 to 34	5 to 14	0.0% (0)	66.7% (2)
Anei and colleagues (2010)	19	34	2	5.3% (1)	57.9% (11)
Total	38			21.1% (8)	47.4% (18)

*GOS ≥4 or mRS ≤3.

Table 2(Abstract A16) Studies applying hypothermia to patients with symptomatic vasospasm refractory to conventional treatment

Study	Number of patients (*n*)	Target temperature (°C)	Duration of hypothermia (days)	Favorable outcome*, % (*n*)	Mortality rate, % (*n*)
Nagao and colleagues (2000)	5	32 to 34	5 to 14	80.0% (4)	0.0% (0)
Nakamura and colleagues (2002)	5	32 to 34	5 to 14	40.0% (2)	60.0% (3)
Nagao and colleagues (2003)	8	32 to 34	5 to 12	87.5% (7)	0.0% (0)
Seule and colleagues (2009)	28	33 to 34	1 to 16	57.1% (16)	28.6% (8)
Total	46			63.0% (29)	26.1% (12)

Note: *GOS ≥4 or mRS ≤3.

Conclusion: So far, the evidence of HT on improved outcome after SAH is limited. Intraoperative HT has been abandoned based on the randomized Intraoperative Hypothermia Study on Aneurysm Surgery in good-grade SAH patients. The available data suggest that HT may improve outcome in a carefully selected subgroup of patients developing intracranial hypertension and/or symptomatic CVS that are refractory to conventional treatment. Further evaluation of cerebral hemodynamics and oxygenation during HT treatment is required to obtain important insights in the effects of HT and to identify patients who may benefit most.

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A17

Hypothermia in the operating theatre

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Critical Care 2012, **16(Suppl 2):**A17

Background: When addressing neuroprotective effects and possible indications of therapeutic hypothermia, several scenarios have to be distinguished. First, therapeutic hypothermia can be classified based on the depth of cooling from normal body temperature into mild hypothermia (32 to 35°C), moderate hypothermia (28 to 32°C), deep hypothermia (28 to 17°C), and profound (<17°C). Second, therapeutic hypothermia can be initiated prior to the insult, for preservation of tissue during the insult, or for the reduction of reperfusion injury after an insult. Third, animal studies and clinical trials have addressed the neuroprotective effects of therapeutic hypothermia under conditions of both global and focal ischaemia. Forth, additional parameters, for example, rewarming rate, duration of ischaemia, and extent of reperfusion, influence the effects of therapeutic hypothermia. Fifth, different outcome measures have been used to describe the effects of hypothermia, for example, infarct size, extent of cellular death, and neurologic condition at different time intervals after ischemia. Therefore, whenever discussing procedures involving therapeutic hypothermia, the aforementioned parameters deserve clarification.

Cerebral ischaemia: Cerebral ischaemia results from a reduction or complete loss of cerebral blood flow (CBF) and lack of cerebral oxygenation, followed by depletion of ATP, dysfunction of ATP-dependent membrane pumps and subsequently occurrence of anoxic depolarisation. A large amount of glutamate is released from the intracellular space into the extracellular space, causing excitotoxic injury by stimulating *N*-methyl-D-aspartate (NMDA) receptors and triggering calcium influx. Increased intracellular calcium levels *per se* amplify injury by increasing calcium permeability and glutamate release via second messenger mechanisms. These acute cascades lead to necrotic neuronal death by interfering with the mitochondrial respiratory chain. Ischaemia and reperfusion further enhance excitotoxicity by providing oxygen as a substrate for several enzymatic oxidation reactions, thereby generating products of reactive oxygen species in large quantities. These free radicals enhance protein oxidation and lipid membrane disintegration and in conjunction with blood-brain barrier (BBB) disruption further contribute to ischaemic necrosis. Apoptosis also occurs in cerebral ischemia, with antiapoptotic proteins being selectively upregulated in surviving neurons and proapoptotic proteins being highly expressed in dying cells.

Hypothermia in cerebral ischaemia: The first controlled attempts to cool the human brain were undertaken by the neurosurgeon Temple Fay in 1938 [1]. Irrigating the brain directly with ice water and sometimes achieving solid parenchymal freezing, he claimed 'extremely gratifying results' in a paper on 'local and generalized refrigeration of the human brain'. Over time, many mechanisms have been proposed regarding the neuroprotective effect of hypothermia. First, hypothermia results in a temperature-dependent decrease of oxygen and glucose metabolism; that is, a 10°C decrease in temperature reduces ATP consumption and the cerebral metabolic rate (CMR) of oxygen, glucose, and lactate twofold to fourfold [2]. Second, intra-ischaemic hypothermia exerts inhibitory effects on many of the detrimental ischaemic cascades, thereby retarding the initial ATP depletion, preserving metabolic stores, delaying anoxic depolarisation, reducing ischaemia-induced excitotoxic neurotransmitter release and intracellular calcium levels, changing glutamate receptor regulation, and limiting BBB breakdown. Busto and coworkers in 1987 reported that even 1 to 2°C temperature reductions were sufficient to protect against experimental ischemic stroke [3], thereby demonstrating that the aforementioned mechanisms can exceed the effects of temperature-induced reductions in CMR, and in turn providing the pathophysiologic foundation for mild and moderate therapeutic hypothermia in the management of cerebral ischaemia.

Indications for therapeutic hypothermia: The importance of therapeutic hypothermia has recently been emphasized by randomised trials in patients with global cerebral ischaemia from out-of-hospital cardiac arrest (OHCA) [4] and in neonates with perinatal hypoxic-ischaemic encephalopathy (HIE) [5]. Clinical experience with patients suffering traumatic brain injuries (TBI) and ischaemic strokes are not as convincing, although mild therapeutic hypothermia was sufficient to control intracranial hypertension in this population.

The use of therapeutic hypothermia in today's OR theatres differs significantly from the scenarios outlined in the context of OHCA, HIE, TBI, or stroke. First, in the OR theatre hypothermia is induced beforehand in expectation of a severe cerebral ischaemic challenge caused by the surgical procedure. Second, underexperienced neuro-anaesthesiologist and cardio-anaesthesiologic management, highly invasive procedures including deep hypothermic cardiac arrest (DHCA) and selective cerebral perfusion can be employed. In other words, whereas outside the OR mild to moderate hypothermia is used to treat patients in the post-ischaemic period, deep intra-ischaemic hypothermia can be used in cardiothoracic and neurosurgery for the management of congenital heart disease, thoracic aneurysms, and intracranial aneurysms; that is, interventions provoking global cerebral ischaemia and otherwise resulting in devastating intraoperative strokes. Moreover, mild hypothermia is used during temporary parent artery clipping in cerebral aneurysm surgery, closely resembling a state of mild intra-ischaemic hypothermia in a condition of transient focal cerebral ischaemia.

DHCA in global cerebral ischaemia: Although DHCA is being used in both cardiothoracic and neurosurgery and usually involves the same principles of extracorporeal circulation under cardiopulmonary bypass (CPB), the rationale behind these procedures is very different.

Hypothermic CPB and DHCA are established strategies of cerebroprotection during cardiothoracic surgery. Cerebral circulatory standstill is an undesired byproduct of this procedure and limits the possible safe duration of surgery. To overcome this problem, methods of retrograde and antegrade cerebral perfusion have been established [6]. Retrograde cerebral perfusion (RCP) was initially considered to extend the safe operative time by both, backward perfusion of the brain via the superior cava vein at pressures of 20 to 30 mmHg, and selective cooling of the brain parenchyma. It has become evident that RCP indeed provides inadequate cerebral perfusion and exerts neuroprotective actions mainly by providing additional cerebral cooling. In contrast, antegrade cerebral perfusion (ACP) is obtained by intermittent infusion of cooled blood directly into cerebral arteries. In detail, selective ACP allows bihemispheric perfusion through direct cannulation of at least two aortic arch vessels, whereas nonselective, hemispheric ACP uses the axillary canula that is used for systemic perfusion as a route for ACP. From the neurosurgical standpoint, not surprisingly, insufficient crossflow across the communicating arteries at the circle of Willis with inadequate perfusion of the contralateral hemisphere has been identified as an important limitation for nonselective ACP. Although a final cooling temperature of 20°C or below with a long cooling time and gradual rewarming are commonly advocated, promising results have been reported by some groups using selective ACP with moderate hypothermia [7].

From the neurosurgical standpoint, the most important information from the cardiothoracic surgical experience is the recommendation that the DHCA time in sole application should not exceed 20 to 25 minutes and in every case with expected DHCA time >25 minutes, ACP or RCP supplement should be performed. In the field of neurosurgery, DHCA combines advanced cerebroprotection with optimal surgical conditions; that is, a blood-free no-flow surgical field and a collapsed aneurysm dome. Since the surgical procedure requires cerebral exsanguination for rapid aneurysm repair, ACP and RCP cannot be employed to dilate the time of DHCA, limiting the safe no-flow period to 20 to 30 minutes.

Management algorithms for intracranial aneurysm surgery under DHCA have been published previously [8-11]. Such advanced cerebrovascular procedures require multimodality neuromonitoring and are performed under barbiturate-induced EEG burst suppression. The decision to use

DHCA is usually made intraopertively; that is, hypothermia and cardiac standstill are employed only after microsurgical exploration has proven that safe aneurysm repair is impossible without these adjunctive measures. In this case, brain retractor placement is adjusted, avoiding further retractor repositioning - with the risk of contusional parenchymal haemorrhage - after systemic heparinisation. Thereafter femoro-femoral percutaneous cannulation is performed and after systemic heparinisation (300 to 400 IU/kg) heart-lung extracorporeal circulation with a heat exchanger and oxygenator is started. Once adequate CPB flow is achieved, systemic hypothermia is induced. Cooling during extracorporeal circulation is continued until a desired brain temperature of 14 to 18°C is reached. Hypothermia results in ventricular fibrillation below 28°C and circulatory arrest at 18 to 22°C. At this point CPB is stopped and blood is actively drained into the venous reservoir, rendering the operative field blood free and the aneurysm collapsed. The duration of this circulatory standstill is limited to the duration of surgical aneurysm repair. In the largest reported series [9], the mean duration of circulatory arrest was 21.8 minutes (range 2 to 72 minutes) with a mean temperature during circulatory arrest of 17.2°C (range 12 to 20°C). The decompressed aneurysm can now be dissected circumferentially, adjacent vital perforating branches can be separated from the aneurysm fundus, and in partially thrombosed lesions the sac can be opened and evacuated. Some centres use short but repetitive periods of circulatory standstill followed by periods of reperfusion, thereby reducing the length of a single ischaemic period and checking for bleedings in the operative field [12]. After aneurysm repair, circulation is restored and under slow rewarming the heart starts to fibrillate spontaneously and will either convert to sinus rhythm or will require cardioversion. Pharmacologic peripheral vasodilation is used to facilitate reperfusion, the blood previously drained is reinfused, and heparin is reversed with protamine. Only after reperfusion, rewarming, and reversal of heparin is adequate hemostasis possible in the operative field.

DHCA was used to treat intracranial aneurysms in the 1960s, but shortcomings of CPB and hypothermia-induced coagulopathies resulted in operative morbidity and declining use of the procedure. In the late 1980s, refined microsurgical and anaesthesiologic techniques allowed the use of DHCA for the management of most difficult intracranial aneurysms in selected neurosurgical centres of excellence [8-11]. With the development of new diagnostic and therapeutic strategies, however, DHCA is only rarely needed for the management of cerebral aneurysms today. Possible explanations include the following. First, easy access to improved neuroradiologic imaging techniques has resulted in the detection of cerebral aneurysms at an earlier stage; that is, before they can grow to giant size requiring the aforementioned surgical procedures. Second, endovascular treatment, for example, flow diverter implantation [13] and techniques of flow reversal, has become an alternative to surgery and should in some instances be considered the first-line treatment; for example, complex and giant posterior circulation aneurysms as well as patients with significant co-morbidities. Third, techniques of cerebral revascularisation - that is, parent artery occlusion under bypass protection - have proven highly effective in the management of complex aneurysms [14]. Forth, alternative strategies for intraoperative aneurysm decompression have been discovered. Adenosine-induced cardiac asystole has emerged as a possible alternative, resulting in brief repeated periods of cardiac arrest (5 to 15 seconds) to facilitate aneurysm clipping [15]. Others have used selective brain cooling with extracorporeal femoral to carotid artery perfusion in giant aneurysm surgery [16], a technique differing from DHCA in so far as the patient's body core temperature is maintained at 35°C and aneurysm decompression is achieved by temporary clipping (trapping) of the parent artery under selective brain cooling to 22°C. Another group has reported successful treatment of a giant basilar artery aneurysm using moderate hypothermia and extracorporeal circulation [12].

Even in expert hands, the procedural complication rate of aneurysm surgery under DHCA is significantly higher than in ordinary aneurysm surgery. The largest published series [9] reports a perioperative mortality of 14% and a combined rate of permanent treatment-related morbidity and mortality of 32%. This recent study, however, reported a contemporary population of patients harbouring complex aneurysms not lending themselves to one of the aforementioned alternative treatment forms. In view of the otherwise unfavourable natural course of these aneurysms, the reported 63% good outcome rate justifies the procedure in a small subset of highly selected patients. For the time being, DHCA should be considered a procedure of last resort for otherwise untreatable aneurysms.

Intra-ischaemic mild hypothermia in focal cerebral ischaemia: The situation of temporary parent artery clipping during cerebral aneurysm surgery closely resembles animal models of transient focal ischaemia, wherein intra-ischaemic hypothermia was more effective than delayed post-ischaemic cooling and was more effective in transient ischaemia and reperfusion models [17-23]. The IHAST trial included 1,001 good grade (WFNS grades I to III) subarachnoid haemorrhage (SAH) patients undergoing aneurysm surgery and randomised them to intraoperative normothermia (36.5°C) versus mild intraoperative hypothermia (33°C). Surprisingly, intraoperative hypothermia did not improve neurologic outcome [24]. Theoretically, the group randomised to mild hypothermia should have enjoyed the cerebroprotective effects of mild intra-ischaemic hypothermia intraoperatively, especially during the ischaemic challenge of temporary clipping. It was subsequently speculated that possibly not all IHAST patients had experienced a significant intraoperative ischaemic challenge and in turn a subgroup analysis of those 441 patients who indeed required temporary clipping was performed [25]. Among these patients, the duration of focal ischaemia - that is, temporary clipping - was the most important determinant of outcome, with those patients requiring temporary clipping of >20 minutes faring significantly worse. Even in this selected subpopulation, mild intra-ischaemic hypothermia did not significantly alter neurologic outcome after intraoperative focal ischaemia. The IHAST results raise the question of how to document relevant intraoperative focal ischaemic challenges and the beneficial effects of neuroprotective interventions in future studies. Even after SAH, gentle surgical manipulation and brief temporary clipping in expert hands were apparently not adequate ischaemic challenges to resemble animal models of temporary focal cerebral ischaemia and reperfusion.

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A18

Temperature management in central nervous infection

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Critical Care 2012, **16(Suppl 2):**A18

Introduction: Brian Kellock quotes in his book *The Fibreman* the seven-year-old (that is, in the year 1918) Denis Burkitt discussing respectfully his uncle Dr Roland Burkitt's legendary reputation amongst his patients in Kenya, Africa, as: '... he believed in curing fevers, in particular in delirious patients, by artificially lowering the patients' temperature ...' [1].
Obviously, Dr Roland Burkitt, the uncle of the legendary Prof. Dr Denis Burkitt, after whom the African lymphoma and its association with Epstein-Barr virus was named, had realized that lowering the body temperature in patients with high fevers, in Kenya highly likely to being due to cerebral malaria, meningitis or encephalitis, might influence positively the course of such potentially - at this time, in many instances, definitely - life-threatening disease [1]. Zdravev stipulated that otogenous brain abscesses not only need to be surgically evacuated but, when causing cerebral herniation, may benefit from lowering body temperature. He was the first to conclude that high body temperature in patients with increased intracranial pressure may be a deleterious association [2].
The wide variety of mechanisms of injury that are exaggerated by hyperthermia and may be ameliorated by moderate hypothermia are described elsewhere in this supplement (see abstract A1). They include mechanisms of neuroexcitotoxicity [3], release of free radicals, changes in blood-brain barrier and vascular permeability, the release of proinflammatory mediators, drawing leucocytes across the blood-brain barrier, increasing the number of inflammatory cells in the brain tissue and the passage of neutrophils, phagocytes, monocytes and macrophages into the brain, additionally injuring neuronal cells by stimulating further immune reactions [4]. Whether interfering with these mechanisms by moderate hypothermia may reduce secondary insult onto neuronal cells and brain tissue is still a matter of discussion. What has been known for long time is that increased intracranial pressure, as frequently seen in viral encephalitis, severe bacterial meningitis and/or brain abscesses, may be modified by therapeutic hypothermia/targeted temperature management [5]. In addition, long-term morbidity and mortality in CNS infection may additionally deteriorate if bacterial meningitis is complicated by cerebral infarction, occurring during the course of disease [6]. Thus, preventing cerebral infarction may be an important tool in reducing both morbidity and mortality in adults with community-acquired bacterial meningitis.
Prandini and colleagues have shown that mild hypothermia reduces remarkably polymorphonuclear leucocyte infiltration in induced brain inflammation in rats compared with those without hypothermia [4].
After any type of brain injury, in particular, ischemic and ischemia reperfusion injury, the reduced brain oxygen supply quickly leads to a decrease in ATP and phosphocreatine levels, thus initiating a complex cascade of events involving excessive calcium influx into brain cells, excessive glutamate receptor activation and neuronal hyperexcitability; that is, triggering off the excitotoxic cascade [3]. Exactly this excitotoxic cascade may be responsible for provoking overt or subtle epileptic seizures in patients with CNS infection, thereby deteriorating the prognosis of these patients. Irazuzta and colleagues could nicely show that in rabbits hypothermia decreases excitatory neurotransmitter release in bacterial meningitis, in particular, the release of glutamate and aspartate, known to be involved in the pathogenesis of neuronal injury in meningitis, suggesting that hypothermia may attenuate excess neuronal stress in this disease [3].
Febrile refractory status epilepticus may be caused by presumed encephalitis carrying a very high morbidity and mortality rate [7]. In addition, it is believed that hyperthermia aggravates brain damage due to continuing epileptic activity. In a retrospective analysis Nakagawa and colleagues found a significant improvement of outcome in children with such febrile refractory status epilepticus who were treated by therapeutic hypothermia with subsequent prophylactic normothermia compared with those children with the same disease but treated only by conventional therapy without fever management [7]. The authors conclude that treatment with therapeutic hypothermia plus subsequent prophylactic normothermia may reduce neurological damage in such patients with severe acute encephalopathy due to refractory febrile convulsive status epilepticus. Another Japanese group treated an adult patient with influenza type A virus-associated encephalopathy with routine therapeutics as oseltamivir and methylprednisolone pulse therapy. Because of severe brain swelling, hypothermia was added. This combination treatment led to full recovery without neurologic sequelae [8]. A similar observation has been reported in 43 children with acute inflammatory encephalopathy and/or encephalitis, out of whom 27 were treated with mild hypothermia. These 27 children were compared with 16 similar patients who were cared for at normothermia levels [9]. The effect of therapeutic hypothermia for children with acute encephalopathy/encephalitis was observed to be dependent on the timing when cooling was initiated. Early cooling (within 12 hours of initial neurological signs of encephalopathy/encephalitis) improved outcome whereas delayed cooling (after 12 hours) tended to be even deleterious [9].
In adults, therapeutic hypothermia in CNS infection has been limited to single case reports and case series. Cuthbertson and colleagues reported induced hypothermia, together with barbiturate coma, in a meningitis patient associated with intractable raised intracranial pressure. Throughout the entire period of mild hypothermia (35°C), achieved by thiopental and external cooling, cerebral perfusion pressure was maintained above 70 mmHg. Barbiturate-induced coma and induced hypothermia were continued for 48 hours when complications (pancreatitis, ventilator-associated pneumonia) prompted one to stop these two therapy modalities. However, the patient remained without any ICP rebound, eventually being weaned from the ventilator and making a rather uneventful recovery, being discharged home with reportedly no neurologic deficits 3 weeks after the disease had began [5]. Similarly, a case with space occupying herpes

simplex virus encephalitis has been reported by Wagner and colleagues. The authors correctly state that conventional intracranial pressure-lowering modalities are limited in such severe herpes simplex virus encephalitis patients and more aggressive treatment options are needed. They induced moderate hypothermia (33°C), resulting in fast and sustained control of intracranial pressure. Eventually the patient regained a relatively good functional outcome, being able to walk unassisted (GOS 4). It needs to be noted that rewarming was done very slowly (1°C/day); that is, over a period of 4 days [10].

Very recently two larger cases series have been published on the use of therapeutic hypothermia both in adult viral meningoencephalitis and in adult community-acquired meningitis by the same Croatian group:

Therapeutic hypothermia in adult viral meningoencephalitis [11]: Eleven adult patients with viral or presumed viral encephalitis (two TBE, two HSV, one VZV, six unknown) pathogen were treated with mild hypothermia, rectal temperature aimed to be 32 to 34°C. The authors, however, do not elaborate on rewarming, speed of rewarming and any adverse effects of rewarming. Remarkably only one patient (1/11 = 9%) died, 3/11 recovered fully, 2/11 with only minor impairment and 5/11 with moderate to severe residual neurological deficit. All patients showed severely impaired GCS at admission (median GCS 8 (range 3 to 10)) and median Acute Physiology and Chronic Health Evaluation score (APACHE) being 24 (range 12 to 32). A major drawback of this study is the lack of ICP monitoring, sonographic measurement of optic nerve sheath diameter having been used as surrogate markers for ICP, both methods not being as reliable as continuous ICP and CPP monitoring. The mortality rate of 9% in this case series compared with 29% in patients with viral meningoencephalitis treated in their unit before implementation of the therapeutic hypothermia protocol. The authors suggest that in carefully selected patients, carefully regarding vasoreactivity status, and, of course, only in those with initially reduced cerebral perfusion pressure, therapeutic hypothermia may be a tool to reduce long-term morbidity and mortality.

Therapeutic hypothermia in bacterial meningitis [12]: The same Croatian group presented a series of 10 patients with severe bacterial meningitis (nine patients: pneumococci, one patient: *Escherichia coli*) with an initial median GCS of 6 (range 3 to 9), APACHE II ranging from 22 to 34 (median 31). They employed the same protocol of non-invasive ICP monitoring (using transcranial Doppler sonography, optic nerve sheath diameter sonography and jugular bulb oximetry). Hypothermia was induced by intravenous infusion of cold isotonic saline and maintained with continuous venovenous hemofiltration at 32 to 34°C. Nothing is said about rewarming, rewarming speed and duration of hypothermia. Two patients died within 48 hours from admission because of refractory intracranial hypertension, two more patients with severe residual neurological deficits (GOS 2) died later on, after discharge from the ICU, because of late-onset nosocomial sepsis; in total, a rather high mortality rate [13,14]. The surviving six patients had a mean ICU stay of 22 days (range 8 to 36), two had a severe and two a moderate residual neurologic deficit. Two of the entire group of 10 patients with bacterial meningitis had a complete neurological recovery (GOS 5).

The authors discuss hypothermia as a neuroprotective measure in severe bacterial meningitis. In nine (out of 10) patients pneumococci were isolated as the causative organisms; however, the authors do not elaborate whether these patients - qualifying early for dexamethasone treatment, in particular, since they showed severe clinical signs and symptoms of increased intracranial pressure - had been given dexamethasone or not. They discuss that corticosteroids have not substantially changed disease outcomes among patients with most severe pneumococcal meningitis. Exactly this aspect is in contrast to the widely accepted knowledge and level of evidence respectively. Recently a meta-analysis has clearly shown that European patients with pneumococcal bacterial meningitis (aged >55 years) definitely benefit from the adjunctive application of dexamethasone [15]. Only one single patient would not have qualified for this definition (47-year-old female being severely immunocompromised). This might explain the high mortality rate despite the administration of the adjunctive therapy with moderate hypothermia. The authors correctly claim that any adjunctive therapy should be continued beyond the very first hours and days since it has been known that in severe bacterial meningitis vasculopathy leading to ischemic stroke may ensue even days after onset. Adequate maintenance of sufficient cerebral perfusion pressure until recovery of CO_2 reactivity (not to be expected before day 4 after initiation of antibiotic treatment) is essential and requires therapeutic hypothermia to be maintained for this period of time. However, the results of this pilot trial in 10 consecutive patients do not justify one to recommend therapeutic hypothermia as adjunctive therapy in bacterial (pneumococcal) meningitis. Whether selected patients with either intractable ICP, dangerously low CPP or infection-associated refractory status epilepticus benefit from moderate hypothermia needs to be elucidated; today this is still a case to case decision.

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A19

Complications of hypothermia: infections

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Critical Care 2012, **16(Suppl 2):**A19

Background: Therapeutic hypothermia (TH) is a very elegant way of inducing short-term and long-term neuroprotection in various disease entities. It has become the standard of care after cardiac resuscitation with an impressive outcome improvement in prospective randomised trials. However, by a broader use of this sophisticated measure the critical care community has become aware of potential side effects limiting its effect on patient outcome. Among others, an increased rate of infections is observed under therapeutic hypothermia and controlled normothermia. The pathophysiological considerations by which TH increases infectious complications comprise reduced inflammatory response and suppression of leukocyte migration and phagocytosis. All together, these observations justify a high vigilance towards infectious manifestations if temperature modulation measures, namely therapeutic hypothermia and controlled normothermia, are used in critical care patients.

Pathophysiological considerations about hypothermia and infections: Intriguing data derived from animal models showing a potent neuroprotective effect in various disease entities induced by hypothermia gave way to a broader use of this method in humans. Thus, therapeutic hypothermia has become the standard of care after cardiac resuscitation as studies demonstrated its strong neuroprotective effect and neurologic outcome improvement [1,2]. It is now recommended by the European Resuscitation Council and the International Liaison Committee on Resuscitation in cases of comatose adults with spontaneous circulation after out-of-hospital cardiac arrest (OHCA) [3]. However, in indications other than resuscitation, such promising results could not be achieved in prospective trials shifting the scientific focus on possible side effects of TH [4-6]. Rewarming injury, shivering, electrolyte dysbalance, pharmacological and pharmacodynamic alterations, cardiovascular effects including arrhythmia, insulin resistance and infections have recently been attributed as limitations occurring in a dose-dependent fashion under TH [7]. Taken together, maximal reduction of these side effects should be a treatment goal if dealing with temperature control measures irrespective of the target temperature. Today, infectious complications are thought to be one of the major contributors limiting the effects of hypothermia [7-12]. Thus advancing diagnostic approach, prevention and treatment of these infectious complications is a great concern of the scientific critical care community and need to be addressed in future prospective trials. In various studies enrolling patient populations suffering from such different diseases as traumatic brain injury, ischaemic stroke or resuscitation post cardiac arrest, an increased rate of infections under TH was observed [4,6,11]. Whether this negative effect has to be attributed to a specific cooling measure remains under debate; however, this hypothesis is unlikely as increased infections are found under both endovascular and surface cooling measures.

The biological interpretation of the pathophysiological backgrounds is challenging as temperature modulation inhibits various inflammatory responses on different levels that are only partly understood today [7,8]. Hypothermia impairs the secretion of proinflammatory cytokines and suppresses leukocyte migration and phagocytosis [7,8]. Recently it has been speculated that hypothermia may induce insulin resistance leading to hyperglycaemia possibly promoting infection onset [8,13].

However, increased rate of infections has also been observed not only under TH but also under endovascularly controlled prophylactic normothermia in patients with severe cerebrovascular disease [10,14]. A significant increase of infectious complications was observed in the endovascular treatment group although TH was strictly avoided. Importantly in this study from our group, analysis of the inflammatory parameters revealed a significant increase of C-reactive protein (CRP) in the prophylactic normothermia group whereas procalcitonin (PCT) and white blood cell count were not elevated [10]. This is a crucial point as it might indicate that temperature modulation may influence the prognostic value of inflammatory parameters [10].

In a retrospective review by Mongardon and coworkers including 421 patients being treated after cardiac arrest, in 281 patients (67%) an infectious complication was diagnosed [11]. Pneumonia was the most frequent, followed by bloodstream infections and catheter-related infections [11]. Gram-negative bacteria were the most frequently isolated infectious germs, but the main pathogen detected was *Staphylococcus aureus* [11]. The high rate of reported pneumonia raises the question of whether intubation at an early stage should be considered in patients under TH to minimise the risk of aspiration.

Is this surcharge too much and how can we minimise it in clinical routine?: Hospital-acquired infections lead to secondary injury in patients and are responsible for a considerable cost increase especially in critical care patients [15,16]. An increased rate of infections under controlled normothermia and therapeutic hypothermia has been described in patients suffering from ischaemic stroke, traumatic brain injury, spontaneous subarachnoid haemorrhage, post resuscitation and intracerebral haemorrhage [6,9,10]. If this observation is associated with significantly impaired outcome or even mortality is under debate [6,9-11]. However, there is general consensus that infections lead to prolonged ICU treatment, secondary injury and lastly to cost increase with significant global economic burden [15]. Therefore, the critical care community has to find effective strategies to minimise the risk of infection complications.

Temperature modulation by any means has to be combined with a standard operation procedure including: routine microbiological surveillance including blood, urine, respiratory specimen work-up; radiological pneumonia surveillance; daily monitoring of inflammatory parameters (CRP, PCT, leukocytes); routine check of catheter insertion sites and timely catheter replacement; avoidance of hyperglycaemia (under TH) and hypoglycaemia (while rewarming!); and monitor performance of cooling device as a high cooling power/rate might indicate fever even if the body core temperature is normal or even <36°C.

Conclusion: These observations justify a high level of vigilance towards infectious manifestations if temperature modulation measures, namely therapeutic hypothermia and controlled normothermia, are used in critical care patients. Whether, at all, the early use of antibiotics in case of suspected infections under TH is justified has to be addressed in future prospective trials.

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A20

Hypothermia and coagulation

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Critical Care 2012, **16(Suppl 2):**A20

Introduction: The effects of hypothermia on coagulation may represent a two-edged sword in patients with acute brain injury who are treated with

therapeutic cooling. On the one hand inhibition of coagulation can have positive effects, such as improvements in the microcirculation and inhibition of the formation of harmful microthrombi in the brain [1]. On the other hand this could lead to increased bleeding risk and thereby cause harm to patients, especially if they have suffered traumatic injuries or are actively bleeding for other reasons. This manuscript will briefly discuss what is known about the effects of hypothermia on cooling.

***In vitro* and experimental data:** The effects of hypothermia on coagulation have been studied mostly *in vitro*. Very mild hypothermia (down to 35°C) has no effect on any part of the coagulation cascade. Temperatures below 35°C can in some cases (but not in all patients, see below) induce mild platelet dysfunction and sometimes a mild decrease in platelet count. When temperatures drop below 33°C other steps in the coagulation cascade, such as the synthesis and kinetics of clotting enzymes and plasminogen activator inhibitors, can also be affected [2-8]. Recently, Ruzicka and coworkers performed a study in which they precisely measured thromboelastography in healthy subjects at a temperature range starting at 38°C all the way down to 12°C [9]. They reported that decreasing temperatures led to a progressive delay in the initiation of thrombus formation, as well as a decrease in the speed of clot creation and growth. However, significant effects of hypothermia on this parameter began only at 30°C, progressing rapidly below this temperature but reaching statistical significance only at 24°C [9]. These authors also found that once clot formation had been completed, the stability of the clot could no longer be influenced by hypothermia; that is, the clots once formed remained stable regardless of temperature. Of note, there was significant interindividual variability in the response of the coagulation parameters to cooling [9].

Hanke and coworkers [10,11] reported that the anticoagulatory effects of hypothermia were markedly increased if acidosis was present, that the effects of hypothermia could be effectively reversed by administering DDAVP and fibrinogen, but that these drugs worked well only if acidosis was corrected [10].

Finally, a number of animal studies have looked at the effects of hypothermia on hematoma formation in models for intracranial hemorrhage and subdural hematoma [12-16]. These studies have not found any evidence for increased hematoma growth or bleeding risk associated with mild hypothermia; in fact, the opposite effect (decreased hematoma volume and vascular brain edema) was observed in most of these studies [12-16]. Indeed a randomized clinical trial is currently being organized to test the safety and efficacy of cooling in patients with intracranial hemorrhage [17].

Clinical studies: The clinical effects of mild hypothermia on bleeding appear to be minor, and clinical studies suggest that the risk of severe bleeding associated with mild hypothermia is very low or even absent. None of the large studies in cardiac arrest, stroke, or traumatic brain injury have reported significant increase in bleeding risks associated with therapeutic cooling, although it should be emphasized that actively bleeding patients were excluded from these studies [12].

Preliminary data suggest that hypothermia can even be used safely in combination with thrombolytic therapy. Hemmen and colleagues performed a prospective controlled clinical trial in 58 patients with acute ischemic stroke, 28 of whom were treated with hypothermia (33°C) combined with thrombolytic therapy [18]; they found that the risk of hemorrhagic conversion did not increase in patients treated with both hypothermia and TPA compared to those treated with TPA alone, and in fact the risk of symptomatic ICH trended to be lower in cooled patients [18].

Spiel and colleagues studied the effect of hypothermia induced by cold fluid infusion in cardiac arrest patients; they reported only slightly prolonged clotting time as measured by rotation thrombelastography [19].

Storm and coworkers compared risk and severity of bleeding in cardiac arrest patients treated with mild hypothermia and thrombolysis to matched historical patients treated with thrombolysis only [20]. They found that the incidence of bleeding was not increased by hypothermia, although there was a trend towards more red blood cell units being required to reach target hematocrit in hypothermic patients who *did* develop bleeding complications. As neurological outcomes were significantly better in patients treated with both thrombolytics and hypothermia, even in those who developed bleeding complications, the authors concluded that bleeding risks should not be viewed as a reason to withhold hypothermia treatment [20].

Tuma and colleagues performed a retrospective analysis from a trauma registry database and identified patients who had developed cardiac arrest and had been treated with hypothermia [21]. The number of patients was small but they found no increased complication rate from hypothermia, in particular bleeding, in their patients. This is noteworthy as hypothermia has gained a negative reputation among those treating multi-traumatized patients, and is seen as one of the factors in the 'lethal triad' of shock, acidosis and hypothermia [22]. The discrepancy may be explained by the interplay between acidosis and hypothermia, as explained above; the effects of (deep) hypothermia on coagulation are pronounced, and difficult to reverse, mainly if there is simultaneous acidosis [22]. However, in the absence of acidosis the effects of hypothermia are much less pronounced, and far more easily controllable and reversible. Most patients undergoing elective treatment with mild hypothermia will not have severe acidosis, and therefore effects of hypothermia on coagulation will be minimal.

These clinical data and the physiological effects of cooling should be taken into account when decisions are made on whether or not to use hypothermia in patients who are actively bleeding, or who are at high risk for bleeding. If possible the (potential) source of bleeding should be (surgically) controlled before cooling is initiated. If this is not possible the risks of bleeding should be weighed against the benefits of cooling, and careful consideration should be given to the depth of hypothermia induced in that patient. Because very mild hypothermia (35°C) does not affect coagulation in any patient this temperature can be safely induced even in patients with very high bleeding risk. At temperatures below 35°C some patients may begin to have mild platelet dysfunction (although in most patients this will occur only at lower temperatures). These effects will be significantly magnified in the presence of acidosis.

In my hospital patients who are admitted after cardiac arrest will usually be cooled to 32 or 33°C for a period of 24 hours, followed by slow rewarming over 16 to 24 hours. If such a patient has concomitant severe traumatic injury (for example, blunt abdominal trauma) and/or has injuries that pose a high bleeding risk that cannot easily be surgically controlled (for example, liver laceration), this patient typically would be cooled to 35°C, and cooling would be continued for 48 or 72 hours instead of our current standard of 24 hours. Similarly, if a patient develops severe uncontrollable bleeding during hypothermia therapy (for example, major upper GI bleed with hemodynamic instability) we would consider rewarming this patient to 35°C (or maintaining 33°C and giving platelet transfusion). In mildly elevated bleeding risk we will cool the patient to 33°C and will treat with platelet transfusion and DDAVP if bleeding complications occur (unless there are severe counter-indications such as recent stent placement).

Of note, it is unknown whether decreasing the intensity of cooling while extending the duration of therapy will provide similar benefits as applying treatment according to published guidelines [23]. Therefore, of course those not at high bleeding risk should be cooled to between 32 and 34°C as current guidelines recommend [23].

Conclusion: Although mild to moderate hypothermia has some effect on the coagulation system the clinical risk of bleeding associated with cooling appears to be very low. This will, however, increase significantly if the patient has moderate-to-severe acidosis. No effects of hypothermia on coagulation occur in any patient as long as temperature is ≥35°C, and patients at very high bleeding risk can safely be cooled to this temperature.

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COOLING IN CARDIOLOGY

A21

Hypothermia in cardiogenic shock

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Critical Care 2012, **16(Suppl 2):**A21

Cardiogenic shock is a state of inadequate systemic tissue perfusion, despite adequate left ventricular filling pressure. It is caused by extensive myocardial damage and appears to be aggravated by a systemic inflammatory response [1-4]. The result is hypotension with metabolic acidosis and often a fatal outcome. The condition affects approximately 5% of the patients with myocardial infarction, and carries a dismal prognosis if it prevails after reperfusion.

Therapeutic hypothermia has several properties of potential benefit in cardiogenic shock: Experiments with isolated myofibrils, papillary muscles and cross-circulated hearts have demonstrated that mild hypothermia increases myocardial contractility [5-7]. In the *in vivo* heart, mild hypothermia has been found to increase stroke volume and cardiac output [6,8].

The increase in contractility is considered to be mediated by an increased myofilament sensitivity to existing Ca^{2+}, without a corresponding increase in myocardial oxygen consumption [9]. Moreover, hypothermia reduces the metabolic rate with 5 to 7%/°C [10,11], thereby reducing the demand on the circulation from the peripheral tissues. In an experimental setting, it also has the ability to reduce infarct size if applied prior to reperfusion [12,13].

In dog-based and porcine-based models of cardiogenic shock secondary to ischemia, therapeutic hypothermia has improved hemodynamic and metabolic parameters, and reduced mortality [14,15]. No randomized controlled trials of therapeutic hypothermia in cardiogenic shock in humans exist, but case series indicate that the effects observed in animal experiments can be reproduced [16-19].

In conclusion, therapeutic hypothermia is a promising treatment option for patients in cardiogenic shock that warrants further investigation.

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A22

Reperfusion injury in acute myocardial infarction

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Critical Care 2012, **16(Suppl 2):**A22

Background: For many years it has been shown that the size of a myocardial infarction is not only determined by ischemic damage, but also by reperfusion itself. This reperfusion injury contributes to up to 50% of the final infarct size. Mechanical postconditioning using short periods of ischemia immediately after reperfusion, pharmacologic postconditioning targeted to prevent opening of the mitochondrial permeability transition pore, and hypothermia have been shown to prevent reperfusion injury in animals and to reduce infarct size in smaller studies. Larger studies targeted to reduce heart failure and mortality are eagerly awaited.

Introduction: Since the early 1970s, infarct size has been identified as a major predictor of prognosis after myocardial infarction: infarct size parallels with arrhythmia, heart failure, and mortality [1]. Apart from this finding, infarct size is not only determined by the area at risk; that is, the myocardium perfused by the infarct-related artery. In a seminal work, Reimer and coworkers could show that irreversible myocardial injury, as determined by cardiac myocyte necrosis, progresses as a wavefront from the subendocardium towards the subepicardium [2]. This observation led to the concept that early reperfusion therapy can salvage myocardium at risk from injury. Early reperfusion therapy within the first 3 to 6 hours after the onset of ischemia was, in consequence, rapidly introduced into clinical routine and is now standard treatment of patients with acute myocardial infarction.

In parallel, it was recognized that reperfusion of temporarily nonperfused myocardium itself has effects on cellular integrity [2]. Reperfusion saves viable myocytes. However, it accelerates the disruption of irreversibly injured myocytes, and thereby permits the process of inflammation, phagocytosis, and infarct repair to begin quickly. It leads to interstitial hemorrhage from vessels that are injured by ischemia but are reperfusable at the time of reflow; that is, in the border zone of the infarction. The hemorrhage itself increases the interstitial pressure, which in consequence worsens the tissue perfusion again. Moreover, reperfusion induces severe morphologic alterations of the myocardium such as cardiac myocytes swelling, mitochondrial damage, hypercontracture, and loss of myofibrillar organization [3]. The observation that reperfusion itself influences infarct size has led to the concept of lethal reperfusion injury [2,3]. It became quickly clear that reperfusion injury is not only determined by mechanical factors such as hemorrhage or interstitial pressure. Reperfusion leads to the activation of many signaling pathways that contribute independently to both apoptotic and necrotic tissue injury and thus decrease the amount of viable myocardium (reviewed in [4,5]). The concept of additional myocardial damage is induced by lethal reperfusion injury has been supported by the observation that interventions started before reperfusion can reduce infarct size, as discussed below [4,5]. Studies in animals suggest that lethal reperfusion injury accounts to up to 50% of the final size of a myocardial infarction.

Clinically, reperfusion injury may be seen in four different types of cardiac dysfunction: myocardial stunning - that is persistent mechanical dysfunction despite restored blood flow which is usually reversible within weeks; the no-reflow phenomenon after opening of an infarcted coronary artery; reperfusion arrhythmia; and lethal, irreversible injury of the myocardium. In the recent years, rapid revascularization was instituted to prevent reperfusion injury. From a clinical view, currently there seems to be no potential to further reduce infarct size by faster restoration of blood flow. Therefore other than mechanical strategies to reduce reperfusion injury and in consequence infarct size are highly welcome to improve the outcome of the patients. To further understand potential strategies, the molecular mechanisms contributing to reperfusion injury are of importance.

Signals contributing to reperfusion injury: The signals contributing to reperfusion injury have been recently reviewed in detail [5]. Major contributors are as follows.

Oxidative stress [6]: which is discussed as the oxygen paradox since the reoxygenation of ischemia generates a myocardial injury that exceeds the injury of ischemia alone. Oxidative stress diminishes the cardioprotective effects of nitric oxide, leading to more neutrophil activation, increased levels of superoxide radicals, and diminished myocardial blood flow.

Increased intracellular calcium: occurring secondary to the ischemic damage of the sarcolemmal membranes and to the oxidative stress-induced dysfunction of the sarcoplasmic reticulum [7]. The calcium excess induces cardiac myocytes death by hypercontracture and opening of the mitochondrial permeability transition pore (mPTP), a molecule recently identified as one of the most important targets in reperfusion injury [8].

***The rapid restoration of physiologic pH* during reperfusion:** which follows the washout of lactic acid. This leads to the activation of the sodium-hydrogen exchanger, finally leading to mPTP opening [9].

Inflammation: leading to neutrophil accumulation and their transmigration into the myocardial tissue. These neutrophils cause vascular plugging and release degradative enzymes and reactive oxygen species [10].

In addition to these more traditional factors, the reperfusion injury salvage kinase (RISK) pathway and its effector, the mPTP, have been currently postulated to be centrally involved in reperfusion injury [8,11,12]. Opening of the mPTP, which releases calcium from the mitochondria and leads to intracellular calcium overload, does not occur in ischemia but is a key determinant of the first few minutes of myocardial reperfusion. Some authors discuss that this pathway could serve as the final effector of the above discussed contributors to reperfusion injury.

Treatment in humans: Whereas in animal studies many agents were successful to reduce reperfusion injury, the translation of these results into the clinical setting has been disappointing for many years [5]. Several groups tried to target oxidative stress with antioxidants or nitric oxide supplementation. These trials had negative results [5,13,14]. Comparably, trials of inhibition of the sodium-hydrogen exchanger, which have been successful in animals by reducing the intracellular calcium overload in reperfusion and by delaying pH normalization in the reperfused myocardium, failed in humans [15], as have various measures to reduce the inflammatory damage induced by neutrophils [5]. Trials with metabolic modulation such as glucose-insulin-potassium infusions or magnesium therapy had inconclusive results. Together, these measures addressing the traditionally seen contributors to reperfusion injury were, at least in humans, not successful to clearly reduce myocardial damage.

Some attempts have clinically been done to treat the no-reflow phenomenon. The administration of platelet glycoprotein GP IIb/IIIa blockers or thrombus aspiration improves reflow after vessel reopening, with limited influence of infarct size. Adenosine is widely used to treat slow-flow phenomena in the infarct-related artery. Of note, the administration of adenosine as an anti-inflammatory and vasodilatatory agent during reperfusion could reduce infarct size in humans, making adenosine currently the only clinically used drug which improves both reflow and infarct size. Adenosine, however, did not reduce clinical end points, which was the primary end point of this study [16].

Three strategies are currently discussed as innovative treatment modalities for reperfusion injury in acute myocardial infarction: mechanical postconditioning, pharmacological postconditioning with

substances influencing the RISK pathway and the mPTP, and hypothermia.

Mechanical postconditioning: In 2003, Zhao and coworkers could demonstrate that short periods of ischemia and reperfusion applied immediately after reopening of an infarct-related artery could reduce reperfusion injury and infarct size, a concept referred to as ischemic postconditioning [17]. In animal studies, ischemic postconditioning involves all major contributors to reperfusion injury including the RISK pathway and the mPTP. Various smaller clinical studies showed in humans that repetitive inflations of an angioplasty balloon after reopening of the infarct-related artery reduces infarct size, wall-motion scores and comparable end points [18-20]. A related strategy, which has also shown to be effective in animals and humans, is the remote ischemic postconditioning. Here, transient episodes of ischemia and reperfusion in a remote organ - that is, skeletal muscle - protect the heart from reperfusion injury. A very elegant randomized trial could show that the simple, non-invasive, repetitive inflation of a standard blood pressure cuff in patients with acute myocardial infarction reduces infarct size when applied before the reopening of the infarct-related artery [21]. Given the confirmation of this finding in larger trials, mechanical, remote postconditioning could be an easy and safe measure to reduce reperfusion injury.

Pharmacologic postconditioning: Extensive preclinical evidence showed that pharmacologic activation of the RISK pathway or prevention of mPTP opening reduces reperfusion injury. Some drugs addressing the RISK pathway have been tested in proof-of-concept studies in patients. Of those, inhibition of the protein kinase C-isoform delta with the substance KAI-9803 given into the infarct-related area immediately before reperfusion [22] and administration of high-dose atorvastatin before PCI [23] are the most promising, both showing favorable effects in about 150 randomized patients. Another clinical trial addressed directly the mPTP. In a small pilot trial including 58 patients, the i.v. administration of cyclosporine (2.5 mg/kg), known to inhibit mPTP opening, reduced infarct size and the release of cardiac markers [24]. Due to the limited numbers of patients, however, it is not clear whether those interventions result in the reduction of clinical endpoints.

Hypothermia: For a couple of years, it has been known that in animals hypothermia instituted before the reopening of an infarct-related coronary artery reduces reperfusion injury and thus infarct size [25]. For infarct size reduction, hypothermia has to be instituted before reperfusion [26], whereas cooling directly after vessel reopening is unsuccessful in most cases [26]. It is discussed that hypothermia prevents the reactive hyperemia in early reperfusion.

Few studies examined the effects of hypothermia in patients with acute myocardial infarction. Dixon and colleagues could show that therapeutic hypothermia is safe in myocardial infarction patients, however, without influencing outcomes [27]. Wolfrum and colleagues showed in patients with myocardial infarction subjected to CPR that institution of therapeutic hypothermia before revascularization did not prolong door-to-balloon times [28]. Two yet unpublished studies, the COOL-MI study and the ICE-IT study, showed no effect on infarct size in the total population. However, in patients with anterior myocardial infarction cooled to <35°C at the time of reperfusion, infarct sizes were roughly halved [29]. The treatment of awake patients not subject to CPR is, however, limited due to counter-regulatory processes such as shivering, which leads to increased oxygen demand and workload of the heart. Future studies will test hypothermia in patients with myocardial infarction, using a straightforward adjunctive treatment with buspirone and meperidine to prevent shivering. In this setting, clear treatment protocols are necessary to avoid prolongation of the door-to-balloon time in patients with myocardial infarction.

Problems still to face: Signaling: Some conditions have been identified to inhibit salvage from reperfusion damage like myocardial hypertrophy, diabetes, age, and hypercholesterolemia (reviewed in [30]). All these conditions are associated with limited ability to successfully activate the RISK pathway. Either they increase the threshold of mechanical postconditioning or they abolish myocardial salvage at all. As these conditions are highly present in the patient population, further research may be of relevance to reestablish susceptibility to modified reperfusion strategies.

Timing: All proposed strategies to prevent reperfusion damage assume a relevant amount of reperfusable myocardium that is waiting to be salvaged. All planned measures to reduce reperfusion damage before revascularization should preferably be applied in a very short time.

Infarct size: Hard clinical endpoints can only be met when there is a significant clinical benefit to be achieved. Posterior infarcts or smaller infarcts of the anterior region only affecting small or medium-sized vessels do not go along with high mortality and therefore there are not many lives to be saved by an optimal reperfusion strategy.

Conclusion: Reperfusion injury contributes to up to 50% of the total myocardial damage. In spite of many successful results in animals, the translation into the clinical setting has been disappointing for many years. Recently, mechanical, remote ischemic postconditioning as well as pharmacologic postconditioning with substances addressing the RISK pathway and the mPTP have shown positive effects on surrogate end points in patients. Hypothermia may be another option in the treatment of reperfusion injury. Larger studies exploring the potential of these therapeutic options to influence clinically relevant endpoints are eagerly awaited. Currently, the evidence is insufficient to permit a widespread clinical use of those interventions.

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COOLING: CROSSING BORDERS

A23

Intracranial pressure and hypothermia

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Critical Care 2012, **16(Suppl 2):**A23

Although the neuroprotective potential of hypothermia is well known and has been established experimentally, its clinical use is limited to selected indications [1], as large trials have yielded disappointing results [2]. This has been mainly attributed to the side effects of hypothermia in critically ill patients and problems with rewarming.
Intracranial hypertension is a major problem in neurocritical care and particularly in patients with subarachnoid hemorrhage (SAH) and traumatic brain injury (TBI), causing death if uncontrolled. As trials on prophylactic hypothermia, for example, for TBI have not been successful in improving outcome, its routine use can currently not be recommended. However, there are many literature reports demonstrating enormous efficacy of hypothermia to reduce elevated intracranial pressure (ICP). Mechanisms of action are thought to be the reduction of metabolism and perfusion and the reduction of edema besides others. Studies have indicated that therapeutic efficacy is sufficient for ICP control at mild hypothermia of 35°C, thus minimizing detrimental effects. In desperate clinical situations hypothermia is used to control intracranial hypertension both for TBI and SAH, but it has recently been applied only as a last resort. Other second-tier therapies and surgical maneuvers like decompressive craniectomy have been popularized instead, although their efficacy is still questioned as well. The knowledge and experience with therapeutic hypothermia has advanced in recent years and the problems of side effects and most importantly rewarming can be better addressed [3]. The latter has been a tremendous problem in patients with uncontrollable ICP, as despite its initial efficacy ICP problems recurred, if hypothermia was stopped prematurely. This goes in line with a recent metaanalysis that stressed the importance of prolonged hypothermia (48 hours to 5 days) and of slow rewarming (<1°C/4 hours). As a consequence the Eurotherm3235Trial was initiated to investigate the effect of hypothermia particularly for intracranial pressure reduction [4]. It has to be awaited whether this will foster the use of hypothermia to treat elevated ICP or whether we will stick with the policy of controlled normothermia.

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A24

Rewarming: facts and myths from the neurological perspectives

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Critical Care 2012, **16(Suppl 2):**A24

Standard operating procedures both for scientific study protocols as well as in routine daily practice stress the importance of slow rewarming after targeted temperature management/moderate therapeutic hypothermia (32 to 34°C) [1-3]. The recommended rewarming speed ranges from 0.1 to 0.4°C/hour, the former allowing a minimum of 24 hours to reach normothermia levels whereas in case of the latter the normothermic temperature levels are reached within 6 to 8 hours. It has been well known and it is widely accepted that abrupt temperature changes, with insufficient temperature control methods, cause change in energy expenditure and intracranial pressure and a negative effect onto the cerebral perfusion pressure and cerebral blood flow. In avalanche survivors the so-called afterdrop has been described to be an additional potentially dangerous condition [4,5]; hypercapnia has been shown to increase the core temperature cooling rate in snow burial victims; furthermore, shivering influences both cooling and rewarming and the cooling afterdrop [4,5].
In the rat model the speed of rewarming plays a crucial role in the development of acute lung injury in intestinal ischemia treated with therapeutic hypothermia. Reactive oxygen species have been shown to play an important role in the pathogenesis of various injuries, including brain injury and lung injury [6]. Besides this, inflammatory reaction and nitric oxide levels are clearly influenced both by therapeutic hypothermia and speed of rewarming. It might be surmised that more gradual rewarming and the addition of anti-inflammatory drugs during this period of rewarming [7,8] might add to or even enhance the neuroprotective effect of therapeutic hypothermia/targeted temperature management [9,10]. This assumption is underlined by the findings that biogenic amines that have been demonstrated to protect cells from apoptotic cell death (for example, serotonin and dopamine) protect cells against rewarming-induced active oxygen species formation and apoptosis [11]. Thus, it is correctly hypothesized that adding drugs containing these biogenic amines or releasing endogenously serotonin and dopamine might help to prevent potential negative side effects of rewarming [11].

Most of the knowledge of post-hypothermic rewarming effects has been gained in experimental settings [1,12,13]. More than 10 years ago the neuroprotective effect visualized by amyloid precursor protein positive axonal swellings, quantifying them per unit area and, thus, serving as marker of both pathophysiologic and neuroprotective effect respectively, has been shown to be reversed completely when normothermia was achieved very rapidly within 20 minutes [3,14]. The originally documented axonal protection was not only eliminated by this rapid rewarming but, in fact, the overall burden of axonal damage was dramatically increased, reaching a virtual doubling of the numbers of damaged axons seen per unit area [3]. Not only amyloid precursor protein accumulation but also neurofilament compaction was seen to be exacerbated by rapid rewarming [3].

Besides this and other neuropathological effects there is now clear evidence that cerebral microcirculation, both in traumatic brain injury and in other severe intracranial diseases, is structurally and functionally perturbed and that this perturbation can be attenuated by hypothermia followed by slow rewarming [2,15]. Similar to the situation with axonal injury, discussed above, the hypothermic protection against cerebral microcirculation impairment can be reversed or the injury even exacerbated by rapid post-hypothermic rewarming [2]. In addition, compelling evidence has been found that traumatically induced or hypoxia-induced generation of oxygen radicals significantly contributes to secondary insult onto brain cells but also damaging endothelium and smooth muscle cells [13]. When employing hypothermic intervention followed by slow rewarming, significant vascular protection was provided; in particular, the generation of oxygen radicals was reduced [14]. The protective effect of hypothermia, once again, is not only a function of time of initiating target temperature and overall duration of hypothermia. Even more importantly, all these positive effects are reversed by rapid rewarming enhancing vascular dysfunction following neuronal injury [10]. Povlishock and Wei clearly state that in the context of traumatically induced axonal damage, microvascular dysfunction, and cerebral contusion, any potentially beneficial effect of hypothermic intervention is consistently reversed and the lesion even exacerbated when post-traumatic hypothermia is followed by rapid rewarming [2]. Most likely, both direct and indirect mitochondrial perturbation together with processes mediated by free radicals influence the ensuing biology and pathophysiology. Post-hypothermic rewarming rates and the potential adverse consequences of rapid rewarming are closely observed in the field of transplantation medicine wherein hypothermic organ maintenance and rewarming are integral to successful organ viability and subsequent transplantation. Rapid rewarming is highly damaging in case of liver transplantation, most likely due to rapid ATP depletion, energy failure and oxygen radical production associated with hepatic mitochondrial damage.

Extrapolation from this body of experimental and human medical knowledge clearly indicates/allows the statement that any type of targeted temperature management/therapeutic hypothermia needs to be followed both by very slow rewarming on the one hand and maintenance of normothermia after reaching the normothermia level on the other hand [16-19]. Exactly this aspect of slow/very slow rewarming has been partially neglected in most recently published studies [19,20]; in particular, on therapeutic hypothermia in traumatic brain injury [21]. In view of the ongoing pathophysiologic processes leading to secondary neuronal damage over a period of more than 5 days post trauma, not only that the duration of therapeutic hypothermia but also the speed of rewarming (0.4°C/hour) need to be questioned and might be interpreted as the major cause of the negative study outcome.

Every researcher, when compiling a study protocol, as well as every clinician is strongly advised to accept the impact of duration of hypothermia and speed/rate of rewarming as being crucial elements both in research and clinical practice. Although it might correctly be surmised that the duration of therapeutic hypothermia is associated with the incidence and intensity of complications, the same might hold true for too short a duration and too quick a rewarming rate. Further studies are needed to evaluate various durations (1 day vs. 3 or 5 days, vs. even longer) both in traumatic brain injury but also in other neurologic diseases that trigger off secondary pathophysiological processes such as ischemic stroke (concept of penumbra), spontaneous intracerebral hemorrhage (peri-hematoma edema), traumatic brain injury or spontaneous aneurysmatic subarachnoid hemorrhage with pathophysiologic processes going on for days and even weeks after the acute ictus. In view of these considerations, prolonging therapeutic hypothermia and, in particular, slowing the rate of rewarming might be the crucial clue to achieve the best possible benefit from targeted temperature management/moderate therapeutic hypothermia without counteracting these benefits by too speedy a rewarming rate. In addition, maintaining normothermia after hypothermia and rewarming seems to be essential in order to avoid the negative rebound effects [22,23].

Finally, it needs again to be noted that a too rapid rewarming might lead to vasodilatation, thus aggravating intracranial pressure, reducing cerebral perfusion pressure and leading to a negative effect on overall neurological outcome [1,19].

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A25

Rewarming: facts and myths from the systemic perspective

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Critical Care 2012, **16(Suppl 2):**A25

Introduction: Rewarming is a delicate phase of therapeutic hypothermia (TH). Adverse consequences of rewarming on the whole body may seriously limit the protective effects of hypothermia, leading to secondary injury. Thus, understanding, predicting, and managing possible systemic side effects of rewarming is important for guaranteeing TH efficacy. The aim of this brief report is to describe rewarming effects from a systemic perspective.

Hemodynamics and imbalance in oxygen consumption and delivery: TH linearly decreases the metabolic rate of homeothermic organisms. During the cooling process, tissue oxygen consumption (VO_2) slows by roughly 6%/°C reduction in body temperature [1,2], obeying the van't Hoff-Arrhenius law, which states that the rate of a biochemical reaction is halved for each 10°C decrease in temperature. The reduction in brain metabolism is similar [3].

In contrast, during rewarming, the possible appearance of a mismatch between total body oxygen demand and oxygen delivery (DO_2) [4] has been recognized since the pioneer works of Hegnauer and colleagues on dogs [5] and Bigelow on humans [6]. Bigelow has described this side effect of rewarming as *rewarming shock*: 'This syndrome of acute acidosis, or rewarming shock, was characterized by a progressive decline in blood pH [...] associated with respiratory inadequacy [...]. A fall in blood pressure and tachycardia were features in some cases'. In more recent studies, rewarming shock after moderate TH seems to be a more infrequent eventuality, probably because TH management has been completely changed by the advent of ICUs and a far less hypothermic regimen. The mismatch between oxygen supply and consumption during rewarming could depend on numerous factors, including metabolic rate, abnormalities in oxygen extraction, cardiac output (CO), circulating blood volume, regional blood flow, pH, blood viscosity, and a shift in the hemoglobin dissociation curve. The physiopathology of this side effect of rewarming is not known. Rewarming from hypothermia is such a complex and metabolism-pervasive process to alter all of the possible determinants of a VO_2/DO_2 mismatch. Of the possible determinants of VO_2/DO_2, cardiac dysfunction has been the most investigated. Cooling determines a proportional decrease in cardiac output [1], heart rate, and mean arterial blood pressure, with no change in stroke volume and increased peripheral vascular resistance. During the maintenance stage of TH, the decrease in metabolic rate is equal to or greater than the decrease in cardiac output, and alteration of oxygen delivery is not a matter of concern. Preliminary clinical studies [7] and a recent meta-analysis [8] have shown a decrease in myocardial ischemic injury. Many of the alterations in the cardiovascular system occurring during hypothermia completely reverse during rewarming. Therefore, the rewarming phase could lead to a permanent deterioration of myocardial function and cardiac output. The pathophysiological mechanism underlying cardiac dysfunction induced by hypothermia rewarming has been studied by Tveita's group, first *in vitro* using a rat left ventricular papillary muscle [9] and then *in vivo* [10] in an intact rat model. These studies showed how post-rewarming systolic left ventricular dysfunction can be related to decreased myofibrillar Ca^{2+} sensitivity due to increased troponin C phosphorylation.

In addition, Blair and colleagues [11] and Morray and Pavlin [12] documented an increase in total oxygen consumption to values above prehypothermic controls in a dog model of rewarming after deep hypothermia. The authors suggested many possible explanations for this event. First, heterogeneous blood flow distribution [13] during hypothermia may determine areas of oxygen debt, with decreased or absent perfusion, that become hypoxic and generate lactate. During rewarming, these areas are reperfused and lactate re-enters normal oxidative pathways, consuming oxygen in the process. Second, with a return to normothermia, free radical oxidation [14,15] and inflammatory response to injury [16,17] could resume, leading to nonrespiratory utilization of oxygen and an increase of VO_2 over pre-injury control. Third, shivering can occur during rewarming as a response to deviations from the temperature set point. The shivering response to maintain a constant core temperature is a concerted reaction involving skeletal muscle contraction and peripheral vasoconstriction. When shivering occurs during rewarming, it is associated with increased VO_2 [18,19] and hemodynamic instability [20].

Cain and Bradley 21] and Schumacker and colleagues [22] have described abnormalities of peripheral oxygen extraction in dogs during hypothermia, even with adequate oxygen delivery. An alteration in the temperature transition of oxidative phosphorylation has been documented in an animal model. Leducq and colleagues presented evidence for an abnormal pattern of oxidative phosphorylation control that correlated with a transition in mitochondrial permeability and persisted after rewarming [23]. This phenomenon may cause alterations in oxygen utilization during and after rewarming.

Kondratiev and colleagues addressed the problem of oxygen supply in a rat model of deep hypothermia (15°C) and rewarming [24]. The experiment demonstrated a reduction in cardiac output and oxygen delivery after prolonged deep hypothermia (15°C for 5 hours) compared with less prolonged exposure. The rewarming-related rightward shift of the oxygen hemoglobin saturation curve, which facilitates oxygen dissociation at the tissue level, compensated for compromised peripheral oxygen transport, leading to a stable oxygen supply. Knowing the events causing VO_2/DO_2 mismatch during rewarming is important in this phase of TH for monitoring and assuring adequate cerebral and whole body oxygen delivery. Low oxygen delivery accounts for the development of secondary injury, which limits the safety and effectiveness of TH. With this perspective in mind, we can suggest various measures to limit VO_2/DO_2 mismatch during rewarming.

First, rewarming after TH should be done slowly and in a controlled manner [25]. Eshel, in a rat model of TH, showed how rapid rewarming from moderate hypothermia is associated with more acute hemodynamic alterations compared with slow rewarming [25]. Similar effects were described in humans [26] and pediatric patients [27] undergoing TH for hypoxic ischemic encephalopathy and deep intraoperative hypothermia (27°C), respectively, as well as in the work of Hanhela and colleagues [28] on adults undergoing cardiopulmonary bypass for cardiac surgery.

Second, controlling pain, sedation, and preventing shivering should limit oxygen consumption. Michenfelder and colleagues [29], Rodriguez and colleagues [30], and Zwischenberger and colleagues [31] demonstrated that the suppression of shivering by neuromuscular blockade is an effective method for diminishing VO_2. More recently, Badjata and colleagues [32] proposed a simple shivering grading tool, the Bedside Shivering Assessment Scale (BSAS), developed by assessing the correlation of bedside shivering and systemic metabolic stress quantified by indirect calorimetry. Using clinical observation of muscle involvement, the BSAS provides an accurate representation of shivering-related oxygen consumption. Accurately defining shivering intensity assures the possibility of a stepwise treatment for shivering. We recommend initially managing shivering with nonsedating interventions, such as correcting hypomagnesemia, or a serotonin (5-TH) 1A partial agonist like buspirone or meperidine. Meperidine has been demonstrated to effectively reduce VO_2 augmentation associated with postoperative shivering at a dosage that does not cause respiratory depression [33]. When these first line interventions fail, sedation with short-acting sedative agents and neuromuscular blockade can be used.

Third, oxygen content and transport should be optimized. Anemia and arterial desaturation must be avoided during rewarming. To date, no clinical trials have examined hemodynamic optimization in patients that have undergone TH, least of all during rewarming, and no evidence is currently available to indicate the best strategy for hemodynamic support in such a critical phase. We suggest a strict control of hemodynamics, with the aim of guaranteeing adequate oxygen delivery and avoiding VO_2/DO_2 mismatch, using at least continuous arterial pressure monitoring, volume balance and urine output surveillance, and frequent serum lactate

measurements. In the case of hemodynamic instability, advanced monitoring capable of finer management could be useful. Thus, in this context, echocardiography and goal-directed hemodynamic optimization [34] may have a place. Treatment of systolic left ventricular impairment presents additional concerns. Pharmacological therapy with catecholamines presents substantial limitations [35,36], as the decreased myofilament Ca^{2+} sensitivity during rewarming significantly diminishes β-adrenoceptor effects. In addition, catecholamines determine elevated myocardial oxygen consumption and arrhythmogenesis. A recent study by Rungatscher and colleagues [37] tested the efficacy of levosimendan in improving myocardial dysfunction after rewarming from deep hypothermia in a rat model. Levosimendan, as a Ca^{2+} sensitizer, demonstrated better inotropic and lusitropic effects than epinephrine.

Glycemic homeostasis: Animal models have shown that hypothermia induces alterations in blood glucose homeostasis via several mechanisms: reduced glucose utilization [38], decreased endogenous insulin secretion [39-41], and increased resistance to exogenous insulin [42,43]. In a recently published prospective observational study dealing with glycemic homeostasis during TH after cardiac arrest (CA), Cueni-Villoz and colleagues found a significantly higher mean blood glucose concentration, blood glucose variability, and insulin dose during TH compared with the normothermia that follows passive rewarming [44]. Because the doses of adrenergic agents did not change significantly between the two steps, the authors advocated lower endogenous insulin levels and the development of insulin resistance as an explanation for the findings. The improvement in glycemic control observed during normothermia, despite lower insulin infusion, suggests that progressive recovery towards normal glycemic homeostasis occurred during rewarming. The rate of hypoglycemic episodes correlated with poor neurological outcome and was similar during TH (8%) and normothermia (7.5%), but more frequently in patients who presented with higher blood glucose variability during TH. These data highlight the importance of progressive tapering of insulin doses to avoid hypoglycemia during passive rewarming from TH after CA, especially for patients who exhibited abrupt glucose shifts during TH.

The importance of glycemic control is further outlined in a recent work by Smith and colleagues. The alteration of blood glucose homeostasis is associated with increased ICU morbidity and poor outcome [45]. Passive rewarming from TH increases insulin sensitivity, but active rewarming from cardiopulmonary bypass decreases it. In both settings, rewarming is characterized by a dynamic insulin/glucose ratio; glucose should be checked frequently and insulin requirements promptly adapted to achieve optimal glycemic control.

Electrolytes: Mild hypothermia shifts potassium inside the cells and predisposes the patient to hypokalemia, as well as hypocalcemia, hypomagnesemia, and hypophosphatemia. During rewarming, rebound increases in these electrolytes (particularly potassium) may occur, especially if they were replaced excessively during the cooling period [46]. Hyperkalemia can be prevented by slow and controlled rewarming, allowing the kidney to excrete the excess potassium. In patients with severe oliguria or anuria, renal replacement therapy should be started before rewarming to avoid hyperkalemia.

Systemic inflammation: TH has been shown to suppress ischemia-induced cerebral and systemic inflammation after traumatic brain injury (TBI) in preclinical [47-51] and clinical settings [16]. Following CA and reperfusion, TH is the only effective therapy for increasing survival and decreasing morbidity [52], probably by impairing harmful inflammatory reactions, which characterize systemic ischemia-reperfusion syndrome [53]. In a recent study, Bisschops and colleagues measured the kinetics of inflammatory mediators during TH and rewarming after CA [16]. Proinflammatory IL-6 increased during the TH phase, but values were surprisingly lower after rewarming. Anti-inflammatory IL-10 and IL-1RA did not significantly change over time. Complement and adhesion molecules, an index of endothelial activation, were elevated at admission, fell to low values during TH, and increased again after rewarming, confirming the hypothesis that inflammatory processes reactivate with the increase in temperature [17]. Interestingly, no significant differences were found between artery and jugular samples, confirming that the ischemia-reperfusion phenomenon is not confined to the brain, but affects the whole organism.

Fast rewarming rates have been shown to predict worse outcomes in animal models [49,54,55] due to the rapid reactivation of the inflammatory processes that were set-off by TH. Even if experimental evidence shows the advantages of controlled rewarming, additional clinical studies are needed to determine the optimal rewarming rate and strategy. Several drugs have also been tested recently in cell culture, tissue, and animal models to check their ability to mitigate the detrimental effects of rewarming. Data from Schmitt and colleagues suggest that pretreatment with methylprednisolone increases cerebral cell survival after deep hypothermia [50], but also suppresses important neuroprotective and regenerative processes induced by the proinflammatory cytokine IL-6. Diestel and colleagues focused on endothelial cells [56], which maintain systemic inflammation via cytokine production. Only combined pretreatment with methylprednisolone and tacrolimus inhibited IL-6 secretion. A specific p38 inhibitor was demonstrated to downregulate the unwanted release of IL-6 after cooling and rewarming most effectively. In a rat model of intestinal ischemia, gradual rewarming and administration of dexamethasone improved [48] survival and attenuated ALI after intestinal ischemia/reperfusion injury treated with TH in rats. Alva and colleagues [15] found that metabolic acidosis induced by rewarming was prevented by fructose 1,6-biphosphate (F1,6BP) administration in rats. F1,6BP also protected against oxidative stress induced after rewarming by decreasing lipid peroxidation in the plasma and potentiating antioxidant enzyme activities in erythrocytes. These results may be due to an increase in plasma nitric oxide and leukocytosis after the F1,6BP bolus. Other preclinical studies dealing with the anti-inflammatory safety and efficacy of these drugs are needed before a clinical study can start.

Infections: The most described infectious complication during TH is pneumonia. As most of the pneumonia diagnoses are made during rewarming or after achieving normothermia [57,58], several authors have claimed that rewarming itself should be considered a high risk for infection. However, as the studies cited above adopted TH for 24 hours and achieved normothermia in the following 12 to 24 hours, the occurrence of pneumonia diagnosis during or after rewarming could also be due to latency from inoculation to the clinical manifestation of infection. Moreover, as hypothermia causes an impaired inflammatory response, clinical signs of infection leading to the diagnosis may be fully detectable only after reactivation of the immune system during or after rewarming. Whether more gradual controlled rewarming can reduce the frequency of pneumonia is unclear. In a small case series [59], even very slow controlled rewarming (0.1°C/hour) was associated with a high frequency of pulmonary infection, perhaps because slow rewarming prolongs the total duration of hypothermia.

Coagulation: Mild platelet dysfunction occurs at temperatures <35°C, and some inhibition of the coagulation cascade develops at temperatures <33°C. In TH after TBI [58] and stroke [57], the platelet count can also decrease, which persists during and after rewarming. In neonatal cold injury, death occurring during rewarming has been attributed to massive thrombosis from platelet hyperaggregation [60].

All of these data suggest that, in the clinical setting, attention must be paid to rewarming rates and attaining the target temperature to assure the optimal effects of hypothermia. The rewarming rate is an important variable; slower rewarming rates should be routinely employed to avoid systemic side effects.

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Hypothermia in refractory status epilepticus

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Critical Care 2012, **16(Suppl 2):**A26

Introduction: Status epilepticus (SE) is a neurological emergency with potentially important mortality and morbidity. After refractoriness to general anesthetics, several pharmacological and nonpharmacological options have been described more or less anecdotally. In this context, and despite animal data supporting neuroprotective actions of brain hypothermia and showing its efficacy in SE models, hypothermia targeting a core temperature of about 33°C for at least 24 hours together with pharmacological sedation has been scarcely reported in adults and children. It seems that this approach rarely allows a sustained control of SE, as seizures tend to recur in normothermic conditions. Conversely, hypothermia has a high evidence level and is increasingly used in postanoxic encephalopathy, both in newborns and adults. Due to the thin available clinical evidence, prospective studies are needed to define the value of hypothermia in SE.

Refractory status epilepticus and its treatment: SE represents the second most frequent neurological emergency after acute stroke, and bears significant risks of morbidity and mortality [1]. SE persisting despite adequate doses of benzodiazepines and at least one antiepileptic drug (AED) is considered refractory (RSE) [2,3]; this develops in 23 to 43% of patients with SE. RSE is associated with acute, severe and potentially fatal underlying etiologies, such as encephalitis, large stroke, or rapidly progressive primary brain tumors, and may be accompanied by coma; these factors, together with increasing age, represent the most important outcome predictors [1].

After securing pulmonary and cardiac functions, intravenous administration of a sequence of three groups of drugs represents the mainstay of management [4]: benzodiazepines (the only clearly evidence-based step); classical antiepileptic drugs (AED, mostly phenytoin, valproate, or levetiracetam); and general anaesthetics for RSE. Among anaesthetics, midazolam, propofol, or barbiturates represents the most popular agents, without any hard evidence favoring one specific compound [1]. Anesthetic treatment may lead to various complications (infections, metabolic disturbances, ileus, neuropathy, myopathy, thromboembolic events) [5]; it is therefore necessary to balance these risks with the benefit of rapid seizure control. Generalized convulsive RSE should be treated rapidly with general anesthetics, given the danger of systemic and neurological injury with ongoing convulsions; conversely, nonconvulsive SE without marked consciousness impairment can be approached more conservatively, as these forms are probably not associated with the same risk of injury [1,2,6].

RSE that proves refractory to a first course of general anesthetics implies a (repeated) careful search of the underlying etiology. This condition may be managed in several ways, which mostly rely on small series or case reports [1,7]. Briefly, pharmacological options may include further use of anesthetics (the three aforementioned, ketamine, isofluorane), other AED (for example, topiramate, lacosamide), or ketogenic diet. Reported nonpharmacological approaches span from resective surgery, through vagus-nerve, electroconvulsive or transcranial magnetic stimulations, to mild therapeutic hypothermia (TH).

While the benefits of hypothermia on patients with head injury were already described by Hippocrates [8], TH enjoys an only evidence-based status in the setting of adult and pediatric postanoxic encephalopathy, and reduction of intracranial pressure [9]. Its indication for the treatment of other acute brain disorders, including SE and traumatic brain injury, is essentially anecdotic.

Animal data on hypothermia: Low brain temperature exerts beneficial effects on the cascades involved in acute cerebral injuries; several seminal studies have been recently reviewed [9,10]. Hypothermia reduces brain metabolism and ATP consumption, and leads to decrease of glutamate release, free radicals, oxidative stress, mitochondrial dysfunction and calcium overload. Conversely, brain-derived neurotrophic factor increases; as a result, apoptosis is inhibited. Furthermore, hypothermia reduces reperfusion injury, permeability of the blood-brain barrier, and inflammatory reactions. Of note, most of these mechanisms are involved in the pathophysiology of SE leading to neuronal injury [11]. Various rodent models of SE support the neuroprotective effects of TH, showing (with concomitant benzodiazepines) a reduction of seizure severity in SE triggered by electrical stimulation of limbic structures [12], and mitigation of seizures, brain edema, and cognitive deficits in kainate-induced SE [13]. Temperature lowering before pilocarpine injections (a proconvulsant) protects against SE and apopotosis [14]. However, TH has received very little attention in clinical settings.

Experience in patients with refractory status epilepticus: More than two decades ago, three children with generalized SE were successfully treated with TH (30 to 31°C) and thiopental [15]. Four adults with SE triggered by limbic encephalitis (two patients), hepatic encephalopathy (one patient) and of unknown origin (one patient) were treated with TH (31 to 35°C) co-administered with midazolam; SE was controlled in all, but two patients later died [16]. Shivering was managed by neuromuscular blockade; vein thrombosis and pulmonary embolism were the reported side effects. Another adult with cryptogenic SE was treated with TH (34°C) and thiopental, but she developed paralytic ileus requiring emergency intestinal resection; she survived after further treatment of her RSE [5]. Ongoing seizures in an infant with a severe developmental disorder were controlled by TH at 35 to 36°C, together with ketamine; subsequently, hemispherectomy had to be carried out [17]. Finally, an abstract in Japanese describes an improved functional outcome in 12 children treated with TH (34 to 36°C) and general anesthesia for febrile SE, as compared with 16 treated with conventional therapy, in a retrospective assessment [18]. Reported TH durations are variable, between 20 hours and several days. These case studies suggest that hypothermia may contribute to seizure control. However, its efficacy seems to be only transient: seizures tend to recur in normothermia. TH may thus represent an option in severely refractory SE, but rather to gain some time as to definitively control seizures.

Recently, it has been recognized that postanoxic SE, even with early myoclonus, does not imply an invariably dismal outcome. It seems that SE occurring during TH, mostly as a seizure suppression EEG pattern, does reflect an extremely severe brain damage, and patients are extremely unlikely to survive [19,20]; conversely, SE arising after return of normothermia and in presence of a reactive EEG background, and preservation of brainstem reflexes and early cortical somatosensory evoked potentials, may be successfully treated with the usual therapeutic armamentarium; those cases represent at most 10% of patients with postanoxic SE, and a good functional outcome can be reached [21]. This actually suggests that TH (with moderate midazolam or propofol doses) can be sufficient to transitorily control benign postanoxic SE (corroborating its antiepileptic properties), while it does not prevent a poor outcome in more severe forms.

Conclusion: As there is a lack of clinical evidence, mild TH (32 to 36°C) may represent a therapeutic option for RSE, albeit on a patient by patient basis. Barbiturates should be avoided because of the risk of paralytic ileus (thus favoring midazolam or propofol), and mild hypothermia should be administered for 24 to 48 hours. Repeated controls of cardiovascular indices, coagulation parameters and lactate (metabolic acidosis following severe infections or intestinal necrosis), and clinical surveillance (vein thrombosis) are mandatory. A well-designed, prospective trial appears necessary to assess the exact role of TH in SE.

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Hypothermia and advanced neuromonitoring

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Critical Care 2012, **16(Suppl 2):**A27

Therapeutic hypothermia (TH) improves short-term neurologic outcome and reduces mortality after cardiac arrest (CA) [1]. Neuroprotective mechanisms comprise reduced cerebral metabolic demand [2,3], decreased excitotoxicity [4-7], cell membrane stabilization [8,9], inhibition of spreading depolarizations [10] and cytokine release [11], and preservation of cerebral autoregulation. This concept of neuroprotection led to clinical trials using TH for the prevention of secondary brain injury in patients with traumatic brain injury, subarachnoid hemorrhage (SAH) and ischemic stroke; however, they failed to show any benefit in clinical outcomes [12-15]. This may reflect our lack of understanding of the exact pathophysiologic processes induced by TH and the potential harm through hypothermia and rewarming injury [16].

Advanced neuromonitoring techniques allow online measurement of brain metabolism, cerebral autoregulation, brain tissue oxygenation, and cerebral blood flow (CBF) and provide information about brain function, energy supply and demand [17-19]. Here we will summarize current knowledge about the effects of TH on brain homeostasis after acute brain injury using advanced neuromonitoring techniques and call for more observational trials investigating pathophysiologic mechanisms during TH and rewarming to maximize the benefits of this emerging therapeutic modality.

TH effectively decreases intracranial pressure (ICP) by up to 10 mmHg [12,20-22], whereby mild hypothermia (35°C) seems to be as effective as 33°C [21,23]. Mechanisms include the reduction in metabolic demand and the inhibitory effect on inflammation and free radical production stabilizing the blood-brain barrier and decreasing vasogenic edema [20,24-26].

Cerebral microdialysis allows bedside monitoring of cerebral metabolic changes from the extracellular fluid of the brain [27]. Decreased energy supply, increased demand or mitochondrial dysfunction may result in brain metabolic distress and/or brain hypoglycemia (brain glucose <0.7 mmol/l). Cerebral microdialysis is feasible during TH and sensitive to detect secondary energy failure as indicated by an increase in the lactate-pyruvate ratio (LPR) [28,29]. Therapeutic hypothermia reduces brain metabolic demand for oxygen and glucose and preserves ATP supply to the brain decreasing the risk of secondary energy failure [29-32]. Moreover, extensive cerebral lactate accumulation is inhibited by TH, which ameliorates the deleterious effects on cell membranes and the blood-brain barrier [33]. Increased brain glucose may be found during TH [6]; however, an increased blood glucose variability during hypothermia has been reported [34]. This may negatively affect brain glucose as sudden decreases in systemic glucose have been associated with brain metabolic distress and worse outcome [35]. Therefore monitoring of brain glucose is important to detect brain hypoglycemia and prevent further neuronal damage during TH and the rewarming phase. An additional beneficial effect of hypothermia that has been extensively studied *in vitro* and in animal models is the reduction in excitotoxic neurotransmitter release [4-7,28], thereby inhibiting nitric oxide synthesis and apoptotic pathways [16,36]. A decrease of extracellular glutamate was observed during TH after cardiac arrest and in ischemic stroke patients using cerebral microdialysis [28,37]. In summary, cerebral microdialysis allows monitoring of the metabolic effects of TH after acute brain injury.

Another mechanism how TH may reduce secondary energy failure is a decrease in oxygen consumption through diminished metabolism [2,3], resulting in increased brain tissue oxygenation [25,38]. Brain tissue oxygenation reflects the net effect of oxygen delivery, diffusion and consumption and can be assessed by positron emission tomography, magnetic resonance spectroscopy, near-infrared spectroscopy or by invasive P_btO_2 probes [39,40]. Therapeutic hypothermia below 35°C may impair brain tissue oxygenation through a left-shift of the oxygen dissociation curve, therefore enhancing the affinity of oxygen to hemoglobin, or by decreasing delivery of oxygen to the brain [21,41]. Jugular bulb oxygen saturation ($jSvO_2$) is a global measurement of brain oxygen extraction and is increased during mild TH [31,41], reflecting a reduction in cerebral metabolic rate of oxygen.

Shivering is frequently observed during TH and may abolish the neuroprotective effect of temperature modulation through increase in metabolic demand and systemic and cerebral energy consumption [42]. A shivering-associated reduction in P_btO_2 seems to correlate with the intensity of therapeutic cooling and potentially increases the risk of brain hypoxia [43]. These results imply that the neuroprotective effect of TH may be most beneficial at a temperature not lower than 35°C and shivering should be assessed at the bedside and effectively treated by pharmacological and nonpharmacological means [42].

It is important to note that CO_2 reactivity may be preserved during TH [44]. Therapeutic hyperventilation as TH is used as rescue therapy to decrease raised ICP and unintentional hypocapnia is also commonly observed in patients with acute brain injury [45], which increases the risk of brain tissue hypoxia [38]. Monitoring of brain tissue oxygen or jugular venous oxygen saturation ($jSvO_2$) is recommended for patients with acute traumatic brain injury, where therapeutic hyperventilation is used [46] and is important especially during TH. Preserved cerebral autoregulation seems not to be disturbed during TH and early induction of hypothermia after SAH led to faster restoration of cerebrovascular reactivity *in vivo* [6,47,48].

The rewarming has been considered as the vulnerable phase following TH [42,49,50]. Rapid rewarming and timing in vulnerable phases of the injured brain may abolish the neuroprotective effects of TH through ICP increase, excitotoxicity, increased metabolic demand and derangement of cerebrovascular reactivity [42,51-53]. A report of four patients treated with TH after CA observed an increase in LPR in all patients during rewarming

indicating brain ischemia [28]. Slow and controlled rewarming after moderate hypothermia may prevent ICP increase and glutamate release and stabilize infarct volume [53]. Close monitoring of cerebral metabolism, ICP, CBF and brain tissue oxygenation can help to define the optimal rewarming rate to avoid increases in ICP (recommended rate of 0.1°C) and to early detect an imbalance in energy supply and demand.

Conclusion: In the clinical setting there is still need to further explore the best induction and maintenance method, optimal duration and targeted temperature of therapeutic hypothermia. Due to the complexity of pathophysiologic mechanisms during hypothermia and rewarming, combining different advanced monitoring techniques seems mandatory. Multimodal neuromonitoring guidance may then help to define therapeutic targets and to establish clinical protocols to maximize the benefits of this emerging therapeutic modality.

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Hypothermia and nutrition: at present more questions than answers?

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Critical Care 2012, **16(Suppl 2):**A28

Therapeutic hypothermia (TH) has been recently accepted as a powerful medical intervention for providing neuroprotection to patients sustaining cardiac arrest and hypoxic-ischemic encephalopathy. Further, TH has also been explored as a potential treatment strategy for patients with traumatic brain injury and ischemic or hemorrhagic stroke (for review see [1]). With the widespread propagation of TH as treatment for intracranial hypertension in patients who are refractory to standard interventions [2], induction and maintenance of TH is no longer restricted to the early period (that is, the first 12 to 24 hours) of acute brain injuries but has expanded over several days until rewarming [3]. Therefore, it is evident that, in addition to the disease process itself, TH has a major impact on ICU management such as analgesia and sedation, ventilator therapy, cardiocirculatory support, or artificial nutrition.

Importantly, the significance of nutrition therapy in critically ill patients cannot be overstated [4]. Critical illness typically induces a catabolic stress state proportional to the severity of injury, predisposing patients to serious nutritional deficits coupled with multiple organ dysfunction, delayed recovery and disproportionate mortality [5]. Effective nutrition therapy can play a major role in attenuating the catabolic response and avoiding the harmful effects of prolonged hypermetabolism. International guidelines provide recommendations for timing until initiation of artificial nutrition, administration route, energy targets and type of nutrients in critically ill patients [4,6]. Starting early nutrition within 24 to 48 hours, primarily using the enteral route, is a proactive strategy to reduce energy deficit [7]. Importantly, underfeeding and overfeeding must be avoided, which implies monitoring nutritional delivery to timely identify an increasing energy gap or excess administration [8]. Energy requirements are most accurately assessed by measuring resting energy expenditure using indirect calorimetry; however, this method is not widely available [9]. Instead, guideline targets could be applied, with a cautious initial energy requirement of 20 to 25 kcal/kg/day increasing thereafter in the recovery phase. Enteral nutrition has the advantage of preventing adverse structural and functional alterations of the gut barrier and of improving mesenteric blood flow as well as enhancing local and systemic immune responsiveness [10]. On the other hand, critically ill patients may often have intolerance to gastric feeding [11]. Prokinetic medications may help restore gastric emptying and promote gastrointestinal motility [12]. Persistent intolerance to enteral nutrition selects patients who will require supplemental parenteral nutrition [6]. Another issue in the context of metabolic consequences of nutrition therapy that deserves attention is glycemic control. Both hyperglycemia and hypoglycemia are of particular concern in critically ill patients [13]. However, to date the goal for blood glucose level and whether intensive or a moderate insulin therapy should be employed in these patients, especially with acute brain injuries, is still uncertain [14]. Implementation of a protocol to promote control of serum glucose when providing nutrition therapy is advocated, and a range of 110 to 150 mg/dl (6.1 to 8.3 mmol/l) may be most appropriate [4].

Whether the aforementioned recommendations on artificial nutrition of the general intensive care patient population can also be applied on equal terms to patients undergoing TH is still a matter of debate. Studies addressing the various issues of nutrition therapy in TH are scarce, as evidenced by a contemporary PubMed search including bibliographies of published reviews. So far, data are available on the course of energy expenditure in patients treated with TH suffering from ischemic or hemorrhagic stroke [15,16] and severe traumatic brain injury [2]. In sedated, ventilated patients receiving muscle relaxants a significant decrease in resting energy expenditure ranging at approximately 75 to 85% of baseline values during TH could be demonstrated. Downregulation of cerebral and overall metabolism as well as muscle relaxation has been discussed as major factors of the reduction in energy expenditure [15]. In contrast, shivering, an anticipated consequence and potentially major adverse effect of TH, has been shown to be strongly associated with graded increases in systemic metabolism [16]. This clearly indicates the need for an individualized determination of the optimal amount of energy to be delivered during TH. Further, one has to bear in mind that other (patho)physiological changes might occur in patients treated with TH. During the maintenance period of TH, electrolyte replacement is often needed because of a decrease in serum levels of potassium, magnesium and phosphate. With rewarming, these electrolytes are released from intracellular stores and move to extracellular spaces. Therefore, care must be taken to avoid rebound hyperkalemia [17]. In addition, insulin resistance, which can lead to hyperglycemia, may occur during TH. Again, in the rewarming period insulin sensitivity may increase rapidly, resulting in sometimes marked hypoglycemia if the insulin dose is not adjusted appropriately [17].

In conclusion, many questions regarding the nutrition therapy of patients treated with TH remain to be answered. Further studies that focus on the optimal amount of caloric intake, timing, preferred route of administration and monitoring of nutrition delivery during targeted temperature management are urgently needed.

Competing interests: RB received financial support as speaker's fees from Baxter Austria and Fresenius-Kabi Austria.

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Cite abstracts in this supplement using the relevant abstract number, e.g.: Beer *et al.*: Hypothermia and nutrition: at present more questions than answers?. *Critical Care* 2012, **16(Suppl 2)**:A28