Targeted Temperature Management (TTM 2014)

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MEETING ABSTRACTS

A1
Let’s get started with targeted temperature management
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Cardiac arrest (CA) remains a major cause of death and severe disability worldwide. The ischemic process that follows the cessation of cerebral perfusion and oxygenation, which is further worsened by the reperfusion injury occurring after the return of spontaneous circulation, can lead to severe hypoxic brain damage, resulting in a high rate of poor neurological recovery among CA survivors.

The use of mild therapeutic hypothermia, or targeted temperature management (TTM) as recently suggested [1], has been recommended in CA patients since the publication of two randomized clinical trials in 2002, the results of which demonstrated a significant improvement in neurologically intact survival for comatose CA patients presenting with ventricular fibrillation or ventricular tachycardia [1,2]. Current guidelines suggest that mild therapeutic hypothermia should also be considered in patients presenting with other rhythms, although this has been less well studied [3].

In experimental studies, TTM provided significant cardiac and neurological protective effects through different pathways. Hypothermic mechanisms providing myocardial protection include, amongst all, improved energy production during ischemia, increased calcium sensitivity of myocytes, regulation of mitochondrial oxidative phosphorylation and preserved myocardial vascular autoregulation [4,5]. All of these protective mechanisms would result in increased myocardial contractility. After a post-anoxic injury, TTM may also protect cerebral function through reduced release of excitatory (that is, glutamate and dopamine) neurotransmitters, attenuation of reactive oxygen species production, preservation of the blood–brain barrier, protection of cerebral microcirculation and decrease in intracranial pressure [6,7]. As several pathways are involved in the pathogenesis of extended post-anoxic brain damage, TTM can be considered as a general and nonspecific neuroprotective strategy, which may efficiently attenuate and mitigate most of these mechanisms and potentially improve patients’ neurological outcome. Interestingly, recent studies have underlined not only that the hypothermic phase is important in this process, but that strict control of the patient’s temperature during the first 3 days since hospital admission (that is, rapid achievement of target temperature, a precise control of temperature during the maintenance phase, a slow and controlled rewarming and avoidance of fever for 48 to 72 hours) are key components to enhance TTM effectiveness after post-anoxic brain injury [8].

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References

A2
Cooling methodology: to influence or to control the temperature?
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The 2010 Guidelines on cardiopulmonary resuscitation and post-resuscitation care, based on the landmark studies on therapeutic hypothermia, state that hypothermia can be induced and maintained with inexpensive means such as simple ice packs and/or wet towels [1]. Indeed there is no method that has proven superior for survival or good neurological outcome. However, this approach comes at the price of an increased burden on nursing staff and greater temperature fluctuations. Also such means do not allow active gradual and controlled rewarming.

While effective in contributing to rapid cooling, simple and inexpensive means may result in greater temperature fluctuations and corresponding
modifications in heart rate and electrolyte plasma concentrations. Notably this strategy requires close and constant supervision of nursing staff, a distraction from other important aspects of patient care. Several studies demonstrate that influencing patient temperature will not allow a steady maintenance phase, controlled rewarming and, most importantly, ensuring strict normothermia once rewarming is concluded in patients with evidence of persisting neurological injury [2,3]. In essence, rather than speed it is control that is most desirable. This one of the lessons learned from the recent Target Temperature Management Trial [4]. In this study a less selected population than previous trials was treated at either 33 or 36°C followed by strict normothermia with an automatic feedback device for temperature management. The study demonstrated an extremely high survival rate (approximately 50%) and good neurological outcome regardless of the temperature regimen. Managing temperature at 36°C may overcome many of the contraindications of therapeutic hypothermia at 33°C, but is at the same time more challenging and hardly feasible without automatic feedback devices. Post-rewarming fever is also difficult to manage. Fever is associated with poor outcome. Even if causation has not been proven, normothermia is currently a therapeutic objective of modern post-resuscitation care. Influencing temperature is not enough to ensure strict normothermia. In the Target Temperature Management trial, active temperature management was maintained for a minimum of 72 hours in unconscious patients. In other fields of application of hypothermia, such as traumatic brain injury treatment and research, protocols dictate prolonged temperature management and extremely slow controlled rewarming based on intracranial pressure.

In conclusion, modern treatment protocols advocate management of temperature, and thus control rather than influence, just like strict management of other vital parameters, is considered a standard of care for the critically ill.

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References

A3 Results and generalizability of the Target Temperature Management Trial and future research for patients admitted to intensive care after cardiac arrest

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The Target Temperature Management (TTM) Trial randomized 950 unconscious, adult patients with return of spontaneous circulation after out-of-hospital cardiac arrest (CA) of presumed cardiac cause to strict temperature management at either 33°C or 36°C. Temperature was managed with intravascular or surface cooling devices for 36 hours, while the patients were sedated and mechanically ventilated. Prognostication and decisions on life-sustaining treatments were postponed until 4.5 to 5 days after CA in the general case [1]. There was no difference in the primary outcome: survival until the end of the trial (mortality 50% in the 33°C group and 48% in the 36°C group, hazard ratio 1.06, 95% confidence interval 0.89 to 1.28, p = 0.51) or the secondary outcomes: neurological function at 6 months and adverse events [2]. In a substudy with detailed cognitive assessment, the groups were similar [3]. The TTM Trial has been criticized for imbalances between groups, the long time to reaching target temperature, poor temperature control, the short time to basic cardiopulmonary resuscitation and that wide inclusion criteria might have missed subgroups with potential benefit of the lower temperature. Regarding baseline differences, the adjusted analyses moved the point estimate of the intervention in direction benefit for the 36°C group (hazard ratio 1.14, p = 0.18) [2]. The time to reach a temperature below 34°C was similar to large registries [4] and faster than the most influential previous randomized trial [5]. Temperature depicted with ±2 standard deviations will visually give an impression of imprecision, compared with studies reporting the interquartile range [5]. Time to basic life support was reported for the subgroups of patients having bystander cardiopulmonary resuscitation only and was identical to previous reports [6]. Subgroup analyses did not show signals in favor of any of the temperatures, but may suggest potential harm of 33°C in circulatory unstable patients [7]. In summary, the results of the TTM Trial are generalizable to the majority of patients admitted to intensive care after a CA of a presumed cardiac cause and temperature management at either 33°C or 36°C after CA should be regarded as evidence-based medicine. Taking the confidence limits of the TTM Trial primary outcome into account, comprising potential clinically significant benefit of both 33°C and 36°C arms, further randomized trials of intensive care treated CA patients must be large and forming international networks will be imperative to move the field forward. The TTM Trial highlights that we still do not have the final answer as to how to best manage temperature after CA and that many questions about efficacy and effectiveness remain open.

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References

A4 TTM 2.0
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The professional treatment of the reperfusion syndrome following cardiac arrest and successful resuscitation has improved over the past decade. In 2002 and 2003 mild hypothermia treatment was first recommended by international guidelines following remarkable milestone trials. With growing experience and an increasing number of hospitals implementing hypothermia as standard treatment, technical devices also improved to enhance patient safety. The term target temperature management (TTM) has been introduced by several societies indicating that cooling down is not enough [1]. We are supposed to manage temperature therapy as part of a package of interventions after cardiac arrest [2,3]. As intracranial pressure can correlate with brain and body temperature, modern TTM is about precision as the optimal target temperature is still unknown. This has been shown by the current TTM Trial by Nielsen and colleagues comparing 33°C and 36°C as different target levels without a significant difference in outcome variables [4]. As these results have been criticized in several points, the conclusion can only be that obviously different patient characteristics need a more individual TTM following cardiac arrest. As stated, TTM 2.0 indicates we have reached the next step that includes professional TTM in a large bundle of therapy steps such as early coronary intervention, close monitoring of supportive care and precise neurological prognostication. The way to go is still long as TTM is still underused worldwide [5,6].

If TTM would be seen as a medication or drug, it should be adjusted or dosed depending on the severity of the disease or hypoxic brain damage. Especially, a moderate reperfusion injury will respond and benefit from a medication like TTM compared with a severe and long-lasting hypoxia leading to death despite any therapy. Therefore, a key in the near future will be the early grading of the hypoxic brain damage by a combination of clinical data, biomarkers, advanced neurological monitoring and radiological findings. This might lead to a more personalized and adjusted post-cardiac arrest treatment.

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References

A5 Targeted temperature management: a health economic perspective
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More and more limited financial resources in the health care sector call for an economic evaluation of potential new therapies. The economic evaluation of a new therapy is complex and depends not only on the perspective of the various stakeholders, but also on the country-specific characteristics of various reimbursement systems. From the patient perspective, the costs for new therapies might not be a concern, as long as the insurance system covers the costs. From the hospital perspective, a new therapy which reduces the length of stay might be worthwhile in a DRG-based reimbursement system, but not in a pay-per-patient-day reimbursement system. To respect the perspective of the society, a cost-effectiveness analysis could be expressed in terms of a ratio where the numerator is a gain in quality-adjusted life years (QALY) and the denominator is the cost associated with the health gain. TTM is a measure of disease burden and takes into account the quality of life measured as the Health Utility Index (HUI, dead = 0 and perfect health = 1) and quantity of life lived measured as survival time: QALY = survival time × HUI (for example, 4 years survival with HUI 0.5 = 2 QALY, or 2 years survival with HUI 1 = 2 QALY).

Previous studies reported that mild therapeutic hypothermia improves neurologic recovery and survival in patients resuscitated from cardiac arrest. The estimated number needed to treat is only six patients; nevertheless, target temperature management has hardly been implemented in post-cardiac arrest treatment. The aim of the current study was to evaluate the cost-effectiveness of therapeutic hypothermia treatment after post-cardiac arrest patients. The QALY-cost ratio was chosen as the primary outcome.

To assess the cost-effectiveness of temperature management, data from a Cochrane review about mild hypothermia after cardiac arrest including 398 patients were analyzed. The QALY-cost ratio was calculated based on the cerebral performance score and total treatment costs after cardiac arrest. The assumed costs included potential cooling procedure, hospital stay, rehabilitation, and potential defibrillation implantation in Austria. Total treatment costs per 100 patients were €4.1 million for patients treated with mild hypothermia, and €3.7 million for patients with standard care. Post-arrest patients receiving mild hypothermia gained an average of 1.11 QALY compared with conventional care. This resulted in a cost-effectiveness ratio of €3,827 per QALY.

Targeted temperature management at 32 to 34°C after cardiac arrest seems to be a very cost-effective treatment, with €3,827 per QALY far below commonly used benchmarks for assessing the cost-effectiveness of an intervention. These results may provide an economic rationale for implementing targeted temperature management as a standard treatment after cardiac arrest.

A6 Side effect management
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Therapeutic hypothermia (TH) induces a parapathological state that can determine clinical modifications which do not constitute necessarily adverse effects, thus warranting monitoring rather than over corrective action in most circumstances. Others are known side effects related to hypothermia and can be anticipated.

Rapid induction of hypothermia by infusion of cold crystalloids with a pressure bag (2 l at 300 mmHg) is associated with an increase rate of pulmonary edema and reaersus (1). The Hypothermia Network Registry reports adverse events of 986 patients treated with TH [2]. Bradycardia was the most common arrhythmia (13%), but pacing was very rarely necessary, suggesting that bradycardia should be tolerated rather than treated if hemodynamic stability is preserved. Pneumonia was the most frequent infection (41%). Bleeding requiring transfusion occurred in 4%; the risk was significantly higher if coronary angiography was performed (2.8% vs. 6.2%; P = 0.02). Sustained hyperglycemia (8 mmol >4 hours) was observed in 37% of patients. Electrolyte disorders were also quite common (18%): specifically hypokalemia, hypomagnesemia, and hypophosphatemia. These derangements should be anticipated, tightly monitored and promptly corrected. The incidence of sepsis was only 4% but was higher in patients with: intravascular devices for temperature management (OR 2.6), intraarticular balloon pump (OR 3.2) or undergoing coronary angiography (OR 4.4). Yet infection, bleeding,
Arrhythmia and electrolyte disorders were not associated with increased mortality.

The Target Temperature Management Trial – the largest trial on temperature management – reported the rate of adverse events as one of the secondary outcomes [3]. There was no difference in adverse events between the 33°C and 36°C arms (respectively 93% vs. 90%, P = 0.086). Among the over 30 subtypes, bleeding, particularly in critical sites, was extremely rare. Bleeding was most common from the insertion sites (33°C, 9.2% vs. 36°C, 6.1%, P = 0.076). Again pneumonia was the most common infection regardless of the level of hypothermia (52% vs. 46%, P = 0.089). The incidence of bradycardia requiring pacing was low and equal in the two groups, suggesting that hypothermia is not responsible for hemodynamically compromising bradycardia (5.2% vs. 6.4%). The only subgroup with a significantly different rate was hypokalemia (19% vs. 13%, P = 0.018). Hyponagmesemia and hypophosphatemia did not differ but were frequent (respectively 20% and 41%), highlighting the need to anticipate electrolyte imbalances.

In conclusion, adverse events can be anticipated and managed. The incidence is not related to the level of temperature management and is not associated with worse survival or neurological recovery.

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References

A7 Shivering management during therapeutic hypothermia in patients with traumatic brain injury: protocol from the Eurotherm3235 trial
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Effective hypothermia in critical care requires a strategy to prevent and manage shivering. Core body temperature in mammals is highly regulated [1]. Hypothermia leads to the activation of measures to counteract this, reducing heat loss through vasoconstriction and increasing heat generation through increased metabolism and shivering. Shivering results in a reduction in core temperature but also increases physiological stresses, including an increase in oxygen demand, catecholamine release and hypertension. It also can appear distressing, may be confused with seizure activity and generally results in monitoring being more difficult.

In the Eurotherm3235 trial [2], the prevention of shivering required that patients were prepared for hypothermia appropriately, that shivering was detected early and that a plan to treat shivering was followed should it be detected. Patients were sedated with an opiate, propofol and/or midazolam because anesthetic agents have been shown to reduce the core temperature set point for shivering. Regular paracetamol was also prescribed as this reduces the hypothermic temperature set point. The hands and feet of patients were covered with towels, which in addition to reducing the risk of thermal burns has been shown to suppress shivering [3]. During hypothermia, patients were observed closely for signs of shivering, particularly in the jaw, neck and trunk as these areas are the earliest to show signs of shivering [4].

On detection of possible shivering, seizures and inadequate sedation were excluded as causes of muscle movements. Specific interventions included active skin counter-warming with forced air convection as mean skin temperature contributes around 20% to the control of autonomic cold defenses, such as vasoconstriction and shivering, and 50% to thermal comfort [3], or the use of pethidine and the 2-agonist clonidine, each associated with significant anti-shivering effects [6].

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A8 Post-cooling fever in post-cardiac arrest patients: post-cooling normothermia as part of target temperature management?
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Experimental studies support that fever after ischaemic brain injury may not only be a surrogate marker for severe cerebral ischaemia but may also deteriorate pre-existent cerebral ischaemic damage and should therefore be treated [1,2]. Neurological damage after cardiac arrest (CA) still determines the final outcome and post-CA critical care focuses on maximal neuroprotection, the application of therapeutic hypothermia (TH). Since the use of TH, many reports have been published on the occurrence of fever post TH or so-called post-cooling fever (PCF). However, the incidence of post-CA fever without TH is similar, ranging from 20 to 78%, suggesting that episodes of temperature >38°C are likely to occur in all patients after CA irrespective of whether TH was administered.

Bro-Jeppesen and colleagues reported a higher 30-day mortality in patients with PCF (temperature >38.5°C) compared with patients without (36% vs. 22%) [3]. Likewise, 1-year unfavourable neurological outcome (43% vs. 27%) was higher in patients with PCF compared with patients without. Maximum temperature and PCF duration were independent predictors of mortality. Their PCF incidence (50.4%, 136/270) was high, probably explained by a longer observation period (36 hours). Leary and colleagues reported a PCF incidence of 41% (69/176) within 24 hours after rewarming [4], while Gebhardt and colleagues reported a 42% incidence (141/336) within 48 hours after CA [5] (both defined PCF as temperature >38°C).

Most importantly, recent data suggest that the effect on mortality becomes significant only with PCF >39°C and a minimum duration of 7 hours. Similarly, Leary and colleagues did not find any effect of PCF on survival and neurological outcome, but a maximum temperature >38.7°C was associated with worse outcome. A prospective analysis of our own post-CA data confirmed this increased mortality in the presence of PCF only above 39°C. In our population of 76 out-of-hospital post-CA patients, PCF between 38 and 39°C did not influence outcome.

The question remains whether we should actively treat (or even prevent) PCF. Many currently applied TH protocols do include a post-cooling period (until 36 hours after rewarming) of induced normothermia (37°C by endovascular or surface cooling) [6]. But is this prolonged normothermia...
practice improving the (neurological) outcome of our patient? There are arguments in favour of a correlation between high PCF (above 39°C) and post-CA outcome. However, whether this high fever is only an epiphenomenon of the severity of cerebral ischaemic injury and whether outcome can be improved by application of strict normothermia in the early post-cooling hours is still undetermined.

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References

A9
Defining dosage
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The landmark studies on therapeutic hypothermia have demonstrated an improved outcome in comatose patients after cardiac arrest targeting a temperature of 33°C for 24 hours [1,2]. The investigated temperature of 33°C was derived from the results of animal studies suggesting the best compromise between neuroprotection and adverse events. In the decade that followed, randomized controlled trials of hypothermia was conducted. Thus, hypothesis-generating data from clinical registries were used to direct future investigations [3]. Surprisingly, data from a large registry of almost 1,000 patients and other observational studies were unable to demonstrate a benefit from the actual depth of temperature achieved, as well as time to hypothermia, time to target temperature, duration of hypothermia and rate of rewarming. This sets the premises and rationale of the Target Temperature Management Trial that investigated two different temperature regimes: 33°C and 36°C [4]. The study demonstrated identical long-term survival, 6 months neurological recovery and rate adverse events between the two temperature groups. This pragmatic trial enrolled a large (939 patients) and less selected population compared with previous randomized studies. When looking at predefined subpopulations again there was benefit of one regimen over the other. Yet a numerical (nonstatistical) trend favors patients treated at 36°C. Most surprisingly, this nonstatistical advantage seems to favor patients likely to be exposed to a more severe injury, such as prolonged time from cardiac arrest to return of spontaneous circulation (median >25 minutes) or shock at admission (respectively HR 1.20 (95% CI 0.96 to 1.50) and HR 1.35 (95% CI 0.90 to 2.03)) [4]. Shock was previously considered an exclusion criterion due to alleged poor prognosis. In this subpopulation, arterial lactate levels were significantly higher in the 33°C throughout the intervention period of 36 hours (P = 0.004) [5]. During the first week of ICU, the extended cardiovascular SOFA score – accounting also for need of vasopressors – was again significantly higher in the 33°C group between days 2 and 4 [5]. Based on the evidence so far available, the most recent Consensus on Science and Treatment Recommendations (Dallas 2015) from the international Liaison Committee on Resuscitation recommends selecting and maintaining a constant target temperature between 32 and 34°C [6]. Whether certain subpopulations of cardiac arrest may benefit from a lower (32 to 34°C) or higher (36°C) temperature remains unknown.

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References
6. [https://volunteer.heart.org/apps/pico/Pages/PublicComment.aspx?q=790].

A10
Prognostication of outcome after cardiac arrest and targeted temperature management
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The vast majority of cardiac arrest (CA) survivors remain comatose at hospital arrival. Around one-half of these patients suffer from severe hypoxic encephalopathy leading to death or unresponsive wakefulness. Early outcome prognostication may reduce futile intensive care and suffering for the patient and their family. Neurophysiologic markers have shown high positive predictive value for poor outcome in patients treated at normothermia, but results may be altered by targeted temperature management (TTM).

Most prominently, absent motor response to painful stimuli 3 days after CA and a serum concentration of neuron-specific enolase (NSE) above 33 ng/ml do not predict poor outcome reliably in these patients [1,2]. Sedation during TTM is a relevant confounder for motor response and corneal reflexes [3]. Bilaterally absent pupillary light reaction 3 days after CA is a reliable predictor of poor outcome (sensitivity 20%) [1]. Eye diseases and medication are potential confounders.

A threshold for poor outcome prediction by NSE has not been established after TTM. Above a level of 80 to 100 ng/ml 72 hours after CA good outcome has rarely been reported. The NSE levels may vary with different test kits, and NSE producing tumors, acute brain diseases and severe hematological diseases/hemolysis are confounders. Bilateral absence of cortical median nerve SSEP remains a reliable predictor, but single cases with recovery were reported [4] and inter-rater reliability is not perfect. Preserved spinal SSEP and low cortical noise levels are important prerequisites. The sensitivity of absent SSEP for poor outcome prediction is around 40% [1]. EEG can be a valuable predictive tool when interpreted by experienced neurophysiologists and indicates (subclinical) status epilepticus [5]. The influence of medication on EEG needs to be considered. Recently, a revised EEG classification has been proposed [6]. A reduced contrast between gray and white matter in brain computed tomography is associated with poor outcome. It can be quantified as
gray–white-matter ratio and values below 1.1 predict poor outcome with high specificity [7]. Additional studies are needed to establish this threshold more firmly. MRI emerges as a prognostic parameter because of high spatial resolution and high sensitivity for cytotoxic brain edema with DWI/ADC imaging [8]. However, access is limited and quantification of early changes needs to be established in larger cohorts.

To date, most authors argue for a multiparameter prognostication approach including repeated neurological examination, SSEP, NSE, EEG and imaging (CT or MRI) combined with a waiting period for potential recovery of several days after cardiac arrest.

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References

A11 Intra-arrest-cooling PRO
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Although targeted temperature management (TTM) has been widely implemented among comatose survivors after cardiac arrest (CA), there are still several unanswered issues, including the optimal time to initiate cooling. Experimental studies have shown that early cooling after return of spontaneous circulation (ROSC) provides better neurological protection than normothermia, while clinical studies failed to show any significant benefits of this strategy [1]. Importantly, several experimental data suggested that hypothermia initiated during cardiopulmonary resuscitation (CPR) – that is, so-called intra-arrest hypothermia (IAHT) – increased the effectiveness of resuscitation attempts and defibrillation when compared with normothermia [2,3]. In a recent systematic review, Scolletta and colleagues identified 23 animal studies and five human studies which evaluated the effects of IAHT in this setting [4]. In particular, animal studies showed that IAHT improved survival and neurological outcomes when compared with normothermia and/or hypothermia after ROSC. IAHT was also associated with improved ROSC rates and with improved cardiac function, including better left ventricular function and reduced myocardial infarct size, when compared with normothermia.

Unfortunately, clinical data on the efficacy of IAHT remain limited. In a retrospective study, Garrett and colleagues compared the outcome for 208 out-of-hospital CA patients treated with intra-arrest cold intravenous fluids with historical controls (n = 334) [5]. The use of IAHT was associated with an increased ROSC rate, while it could not improve overall survival to hospital admission or to discharge. Nevertheless, less than 10% of patients admitted to the hospital were eventually treated with in-hospital TTM, which negatively influenced the effects of early cooling on patients’ outcome. In a recent randomized clinical trial, Debaty and colleagues evaluated the effects of intra-arrest cold fluids when compared with TTM started after hospital admission on out-of-hospital CA patients, irrespective of their initial rhythm [6]. Of the 245 patients included (n = 123 in the IAHT group; n = 122 in the control group), IAHT significantly reduced the time to reach body temperature below 34°C by 75 minutes; however, the proportion of patients admitted alive to hospital was not different between groups (33% vs. 30%; P = 0.51). Levels of neuron-specific enolase, a biomarker of brain injury, which was considered the primary outcome of the study, were not different between groups and no difference in survival and 1-month neurological recovery was found. Importantly, intra-arrest cold fluids are potentially associated with important adverse events, such as a reduced coronary perfusion pressure, a longer duration of CPR and the development of lung edema, which may have ameliorated their beneficial effects [7]. In another randomized clinical trial using intra-arrest transnasal evaporative cooling [8], out-of-hospital CA patients were randomized, irrespective of their rhythm, to receive IAHT (n = 96) or standard of care (n = 104, including in-hospital TTM) during CPR [8]. Overall survival rates were similar in the two groups (15% vs. 13%). Among patients admitted to the hospital, overall survival was increased, although not significantly, from 31 to 44% using IAHT (P = 0.16). Also, IAHT increased, although not significantly (P = 0.14), the intact neurological outcome rate from 21% to 34% when compared with controls; these beneficial effects were more pronounced in patients with short time to CPR (that is, <10 minutes; 43% vs. 17%, P= 0.03). An ongoing randomized clinical trial will include nearly 800 patients to confirm these promising preliminary results using intra-arrest transnasal evaporative cooling in out-of-hospital CA.

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References
The time of initiation of targeted temperature management in cardiac arrest patients is a matter of debate. This article will summarize the evidence for initiation of targeted temperature management already during cardiac arrest, before restoration of spontaneous circulation. Routine care should be based on evidence of high quality. The Grading of Recommendations Assessment, Development and Evaluation (short GRADE) Working Group considers only methodologically valid human randomized clinical trials as evidence of high quality. Only two randomized clinical trials evaluated the benefit of intra-arrest cooling as compared with cooling after restoration of spontaneous circulation [1,2].

The study by Castren and colleagues investigated intra-arrest transnasal evaporative cooling within 20 minutes of the start of cardiopulmonary resuscitation (n = 96). Patients with in-hospital cooling after restoration of spontaneous circulation served as the control group (n = 104). Intra-arrest cooling was feasible and safe, but showed in comparison with in-hospital cooling no statistically significant benefit in the rate of restoration of spontaneous circulation (38% vs. 43%), survival (15% vs. 13%), or good neurological outcome (11% vs. 9%).

The study by Debaty and colleagues investigated intra-arrest cooling with infusion of up to 2 l ice-cold 0.9% saline at 100 ml/minute plus cool pads (n = 123), as compared with in-hospital cooling with cold saline infusion plus cooling mattress, and cold air circulation (n = 122). Overall, intra-arrest cooling showed no statistically significant benefit in survival as compared with in-hospital cooling (5.7% vs. 4.1%). One limitation of this study is that not all patients reached the target temperature of 32 to 34°C for 24 hours. A pooled analysis of the two studies revealed similar results as compared with the individual studies: intra-arrest cooling versus in-hospital cooling risk ratios (95% confidence interval) were 1.6 (0.8 to 3.2) for restoration of spontaneous circulation, 1.2 (0.7 to 2.2) for survival, and 1.1 (0.6 to 1.6) for good neurological outcome.

Although pathophysiology and animal data suggest a benefit of intra-arrest hypothermia over post-arrest hypothermia, routine care should be based on evidence of high quality. Randomized clinical studies do not show benefit of intra-arrest hypothermia on neurological outcome or survival, and thus intra-arrest hypothermia should be restricted to clinical trials and not used in daily practice.

References

A13
Effective temperature management
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‘It is not enough just to influence body temperature – you have to control it’ (M Holzer, Therapeutic Temperature Management (TTM) 2012, Berlin). For this to be possible we need the ideal cooling equipment/technique and a reliable temperature monitoring technique. Many techniques are available [1], but only two types meet most of the ideal characteristics – automatic temperature feedback-controlled surface hydrogel pads or endovascular cooling devices.

To be fully effective, control is needed for all three phases of TTM. Induction – the how and when are to an extent disease dependent. The evidence is only animal based [2] and the human evidence can be conflicting [3], although the suggestion appears to be the sooner the better. Decision to target temperature times are similar for both types of devices, but may be enhanced with the use of adjuncts, such as intravenous infusion of cold fluids. Surface cooling is negatively influenced by obesity and pyrexia, with 32% of patients failing to reach the target in <12 hours [4].

Maintenance – how deep and how long? Some guidance does exist for depth on a disease process basis (for example, 2010 European resuscitation guidelines). Most evidence is available for post-cardiac arrest, cooling to <34°C. However, recent evidence suggests that preventing fever by cooling to 30°C is just as effective as cooling to 33°C [5]. Duration appears to correlate with outcome. Animal studies support this [2] and human studies are suggestive. For TBI, mortality is definitely better but neurologic outcome is less clear [6]. Although each technique has its own advantages, overall both seem equally effective at maintaining a stable target temperature [7]. However, for it to be successful, complications of TTM need to be effectively managed.

Rewarming – often the Cinderella, but it has been long known that it can affect the neurological outcome. The question that has as yet to be answered is how fast? The consensus based on evidence available is that slow is best for the brain but mortality and neurological outcome [6], whilst avoiding post-rewarming fever. Both types of device seem to be able to control rewarming adequately.

So how can you choose which device to use, as each seems to be effective in all three phases? Long-term use of endovascular devices for fever control is associated with a higher incidence of VTE and PE [8], thus, for longer term temperature management the surface device may be the more appropriate.

In conclusion, effective temperature control is essential for TTM, this is best achieved with temperature feedback control devices, and management of complications is an essential part of the care. Is fever control the new goal for post-cardiac arrest and ischaemic stroke?

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References

A14
Common physiological responses during TTM
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Achieving and maintaining perfect homeostasis, particularly in terms of metabolism, represent a major goal for post-cardiac arrest (CA) care. Since cooling may provoke different physiological responses, it is of
particular importance to be aware of these changes that may require specific treatment adjustments during this recovery period [1]. Several points are particularly illustrative. Regarding ventilatory management, induced therapeutic hypothermia (TH) is known to decrease CO₂ production, which may result in deleterious hypocapnia. Blood gases and expiratory tidal CO₂ should be cautiously monitored in order to adapt ventilator settings since pronounced hypocapnia can provoke a decrease in cerebral blood flow that may alter brain perfusion [2]. Conversely, hypercapnia, leading to cerebrovascular vasodilatation and increased intracranial pressure, should also be banned. Regarding metabolic control, the correction of electrolyte and acid-base disturbances is essential and special attention should be given to those that may participate in the recurrence of CA or worsening of organ dysfunction (potassium, arterial pH). Concerning glycemia, consistent data underline that blood glucose variability seriously impairs the outcome of these patients rather than the mean level of glycemia, so attention should be paid to avoid such glycemia fluctuations [3]. Besides severe shock and brain injuries, patients with successfully resuscitated CA are also exposed to infectious complications, a supplementary insult which may affect a large number of survivors. Experimental hypothermia impairs immune functions and inhibits the secretion of proinflammatory cytokines and may suppress leukocyte migration and phagocytosis. In humans, TH is associated with an increased risk of early onset pneumonia [4]. Furthermore, the diagnosis of these infectious events is complicated in patients after CA, not only by the physiological effects of TH but also by the consequences of post-cardiac arrest syndrome. Even if they do not impact on survival or neurological outcome, these infectious events increase the duration of mechanical ventilation and hospital length of stay and should be managed using tailored preventive and therapeutic strategies. Finally, TH might also induce physiological changes in coagulation that may promote acute stent thrombosis. Experimental models showed that hypothermia may induce platelet activation, thrombus formation and stabilization, and several clinical studies reported an unexpected high rate of acute stent thrombosis in cardiac arrest patients after cooling for CA, which may compromise the benefit associated with early coronary reperfusion [5]. On the whole, being aware of all physiological changes induced by TH is crucial in order to maximize the benefit of this treatment in clinical practice.

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References

In cardiac arrest patients the primary goal is to restart the heart, return the patient to life, and keep the brain intact. In 1960 a landmark article described the outcome in CPR [1]. In 1964 Peter Safar published the first integrated approach to cardiac arrest, and recommended therapeutic hypothermia (TH) for support recovery [2]. These two studies merged in the first American Heart Association guidelines for the treatment of cardiac arrest patients [3]. The most recent update of the ERC and American Heart Association guidelines were published in November 2010. The use of TH in cardiac arrest patients developed after two cornerstone studies which showed good neurological outcome when the body temperature decreased to 32 to 34°C after out-of-hospital cardiac arrest [4,5]. Hypothermia can prevent or reduce cellular damage in the post-cardiac arrest period [6]. Current resuscitation guidelines recommend use of TH as soon as possible following return of spontaneous circulation [7]. Most TTM protocols call for induction with cold intravenous saline and surface cooling with cold packs while TH devices are being applied. Since then TTM of 32 to 34°C for 12 to 24 hours has been recommended as part of post-resuscitation care by international guidelines. Frydland and colleagues assessed mild hypothermia in 12 studies in patients with out-of-hospital cardiac arrest and nonshockable rhythms as an initial one [8]. TTM has been recommended for nonshockable rhythms [9]. Some observational studies supported the use of TTM in out-of-hospital cardiac arrest and initial nonshockable rhythms [10,11]. The new resuscitation guidelines will represent the most recent and comprehensive analysis of intubation or supraglottic airway devices, mechanical devices, adrenaline use, telephone CPR, hypothermia/TTM, early PCI, and post-arrest care. In the new guidelines in 2015 there may be answers for the optimal temperature target, duration of TH, and rates of cooling and rewarming for post arrest.

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References
Acute brain injury induces a complicated cascade of deleterious pathways that can be counteracted by therapeutic hypothermia (TH) in the experimental setting [1]. While there is no level I indication for TH in neurology, TH is in principle useful for these indications if applied appropriately.

Ischemic stroke: While fever is harmful in acute stroke, no clinical study showed improved outcome by antipyretic treatment – most likely because of poor antipyretic management [1]. In large ischemic stroke, post-ischemic brain edema and ICP are major therapeutic targets. A limited number of case series indicate feasibility and safety of TH (48 to 72 hours) in large ischemic stroke. However, rewarming led often to rebound or previously well controlled ICP and herniation [1]. Knowing the natural course of edema in large ischemic stroke, the duration of TH was chosen too short to maintain appropriate ICP control. After publication of a successful randomized controlled trial for hemicraniectomy in malignant stroke, TH might remain an experimental therapeutic option in large ischemic stroke which appears in more than the territory supplied by the middle cerebral artery. In this case, TH and hemicraniectomy could be combined and TH should last at least for more than 72 hours. Patients with acute ischemic stroke (>6 hours from onset) might in principle benefit from TH [1,2]. However, available data are limited and showed feasibility and safety of TH, but are underpowered for efficacy. Ongoing stroke trials include 2019 2173 patients who are treated by an individual target temperature of 36 to 33°C [2]. Shivering and discomfort are counteracted by external warming and the use of pharmacological agents (opioids, buspirone, or/dexmedetomidine). So far, both, ongoing trials suffer from slow recruitment which indicates the complex procedure.

Intracerebral hemorrhage: The outcome after large deep ICH is poor. Surgical and medical treatment do not improve outcome essentially. Besides the size of hematoma, the clinical condition is complicated by perihemorrhagic edema, which increases over more than 10 days [3]. Additionally, the size of perihemorrhagic edema is associated with the size of hematoma volume. Two case series showed that early TH (35°C for 10 days) was feasible and safe. TH was able to control ICP and prevented perihemorrhagic edema increase measured by repeated cranial CT. Moreover, neurological outcome and survival were superior compared with a historical control group [3]. At present, a German–Austrian controlled randomized clinical trial investigates efficacy in large ICH.

Subarachnoid hemorrhage: Experimental data showed that TH was neuroprotective in SAH and reduced vasospasm, DCI and brain edema. Clinical data on the use of TH in SAH are limited. In a recent study without a control group, TH was used as a rescue therapy in patients with severe SAH and was feasible [4]. Smaller studies indicate that TH can reduce mean blood flow velocity in vessels with vasospasm and potentially improve outcome including less DCI. In conclusion, TH is still a promising treatment option for acute brain injury. The use of TH has to be adapted to the specific targets of each condition and transferred to clinical studies.

References

A17 Is fever good? What do we actually know?
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In patients with acquired brain injury there is a widely held belief that fever is harmful. However, a critical examination of the literature suggests that these beliefs may be based more on faith and less on science. Cooling the injured brain to prevent further injury makes intuitive sense and is supported by a diverse array of animal studies. However, to date, data from good quality randomised controlled trials proving that therapeutic hypothermia is beneficial are lacking. Indeed the recent Targeted Temperature Management Trial found no additional advantage to cooling below normothermia following cardiac arrest [1]. However, this result would support the argument that the benefit of targeted temperature management is due to the avoidance of fever. On the face of it this hypothesis is supported by experimental studies. However, these tend to employ induced hyperthermia which is quite different from spontaneous endogenous fever.

In clinical studies fever is widely reported as associated with adverse outcomes following cardiac arrest; brain trauma and stroke. However, proving the causality is problematic as this could merely be an association with injury severity through the induction of inflammatory systems [2]. In an attempt to control for such confounding, the technique of multivariable logistic regression is commonly used to suggest that fever is an independent variable associated with poor outcome [3]. However, the prediction of outcome variability depends on the robustness of the model used and so it is always possible that fever captures some aspect of severity that is not captured by other variables.

Whilst there is a clear association between fever and poor outcome following acute brain injury, it should be remembered that that causality remains unproven. Furthermore, and most significantly, there are no trials demonstrating that preventing or treating fever following brain injury improves outcome. Clearly this is an area in need of more scientific study.

Targeted temperature management should be state of the art nowadays after cardiac arrest. With gaining knowledge about reperfusion injury after general hypoxia it became obvious that intensive care treatment contains a bundle of different steps rather than only cooling the patient. In trauma patients, outcome was improved by treatment in high-volume centers with high experience [1,2]. Concerning the overall outcome and length of stay, trauma patients benefit from admission to a trauma center. However, current data show a higher survival rate after cardiac arrest if hospitals treat a large number of survivors [3]. In addition, hospital characteristics such as the capability for a coronary intervention (PCI) 24/7 were shown to have a significant impact on outcome after cardiac arrest [4]. Therefore, the foundation of cardiac arrest centers (CAC) in Germany, similar to the USA, is the corollary [5]. The mission of CAC is manifold. Owing to the high number of patients treated, a written standard protocol and a data registry are essential. High quality and quantity management need to be transparent and reviewable at any time. Besides a structured admission process including, for example, the timing of PCI and/or CT scan, the neurological prognostication process should also follow a predefined, written timeline and standardized diagnostic steps, as this is a very sensitive and complex part of the treatment. Furthermore, CAC are preset for research and participation in international multicenter trials. Especially in cardiac arrest patients, future
questions will only be answered with a high number of patients due to heterogeneity in cause of arrest and grade of hypoxia. Potential additional costs have to be part of a novel reimbursement structure concerning post-cardiac arrest therapy.

CAC are therefore necessary and needed in the near future.

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References