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Sudden cardiac death: Role of therapeutic hypothermia

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Abstract

Permanent neurocognitive deficits due to cerebral sequelae account for the majority of long-term morbidity and mortality in survivors of cardiac arrest today.

Albeit therapeutic hypothermia had been used as effective measure to ameliorate cerebral ischemia-reperfusion injury during surgery for decades, it was not yet introduced into regular post-arrest care until 2003 due to significant side effects of profound hypothermia. These include shivering, higher infection rates, coagulopathy or cardiac arrhythmias, but are less frequently observed with mild therapeutic hypothermia. When body temperature is kept around 33°C, the beneficial effects of hypothermia clearly outweigh its adverse effects. Therefore, treatment of comatose survivors of out-of-hospital cardiac arrest using mild therapeutic hypothermia has now been widely adopted around the globe. Although it still remains controversial who, how, when, and for how long to cool, with only six patients requiring treatment to save one additional life, it is clear that therapeutic hypothermia is the single most effective intervention in brain resuscitation available today.

Key words: cardiac arrest, cardiopulmonary resuscitation, cerebral ischemia, induced hypothermia

Abbreviations

MTH Mild therapeutic hypothermia
OHCA Out-of-hospital cardiac arrest
ROSC Return of spontaneous circulation

Introduction

Despite many advances in primary and intensive care treatment, not even a third of all patients with a return of spontaneous circulation (ROSC) survive until hospital discharge when the cardiac arrest occurs outside a hospital [1, 2]. Furthermore, the primary mode of death in the post arrest period is neurological

failure [1]. Survivors of cardiac arrest suffer from significant neuro-cognitive dysfunction, with a spectrum ranging from minor deficits to brain death. It is apparent that an ischemia-reperfusion injury, coined the “post-cardiac arrest syndrome”, is responsible for the high mortality among these patients [3]. Therapeutic interventions to ameliorate this condition are limited. Recent experimental approaches include the use of volatile anesthetics or inhalation of noble gases. However, mild therapeutic hypothermia (MTH) remains the only treatment that has been successfully introduced into clinical practice to date, and therefore represents the current gold standard in post-arrest care.

This review article discusses pathophysiological basics of cerebral ischemia-reperfusion injury and mechanisms through which MTH is believed to exert its beneficial effects. Furthermore, established cooling strategies and protocols to fight neurological sequelae following cardiac arrest are summarized. Finally, a brief introduction to prospective supplemental therapeutic approaches complements this article.

History of therapeutic hypothermia

One of the first descriptions of induced therapeutic hypothermia was published more than 50 years ago, when intraoperative cooling was used during neurosurgical procedures to ameliorate cerebral sequelae due to temporary ischemia [4] or after cardiac arrest [5]. During this period, target temperatures of 30°C and below were frequently chosen, and soon associated with side-effects such as cardiac arrhythmias, coagulopathy, and increased infection rates. Animal experiments in the 1990's then revealed that mild hypothermia (34-36°C) offers a fairly better safety profile as profound hypothermia (28-32°C) while still showing significant effects in terms of neuroprotection [6]. At the beginning of this century, clinical trials finally revealed that the concept of mild hypothermia with target body temperatures around 33°C following successful resuscitation is effective in survivors of cardiac arrest [7, 8]. This concept is now widely referred to as 'mild therapeutic hypothermia' (MTH).

Together with results from several animal studies [9-12], these findings led to an ILCOR advisory statement in 2003 [13], and finally to the introduction of MTH into international resuscitation guidelines in 2005 [14]. With only six patients requiring treatment to save one additional life, MTH is considered to be the single most effective intervention and therefore the gold standard in post resuscitation care today [15]. However, although MTH has been widely investigated in numer-

ous animal studies and clinical trials, there is still controversy on the particular population that should be treated with MTH, leaving alone questions on the optimal duration and depth of cooling.

Pathophysiology of cerebral ischemia and potential targets for neuroprotection by hypothermia and supplementary drugs

Molecular mechanisms involved in cerebral ischemia-reperfusion injury are fairly complex, but can be roughly split into an acute hypoxemia-induced cell death (necrosis) and a delayed neuronal decay (apoptosis) during and following cerebral reperfusion [16]. The key element determining death or survival of the cell during reperfusion has been identified to be the intracellular calcium homeostasis, which is regulated by a number of receptors, transporters and signaling molecules. The overactivation of the cell by excessive stimulation by neurotransmitters following an ischemic/hypoxic episode, coined 'excitotoxicity', leads to an uncontrolled influx of calcium ions, triggered by accumulating neurotransmitters glutamate and aspartate [17-19]. Other unspecific mediators, such as free radicals and released metabolic products, further aggravate the neuronal damage.

Therapeutic hypothermia had long been thought to unfold its cytoprotective effects simply via unspecific inhibition of catabolic processes throughout the organism during the reperfusion period, translating into a reduction in oxygen and glucose consumption between 5-7% per 1°C [20]. Mounting evidence suggests that other molecular mechanisms are also involved in MTH-mediated neuroprotection following global ischemia.

Possible targets that are known to be affected by MTH are the inhibition of ischemia-induced releases of amino acids such as glutamate and aspartate [21], and through reduction of DNA damage-dependent pro-

death signaling events such as p53 activation [22]. Similarly, MTH blocks delta-protein kinase C and several other proteins associated with apoptotic cell death, including those of the Bcl-2 family [23, 24]. The noble gas Xenon as an example for an MTH-augmenting drug candidate has been found to have a considerable effect on these targets. Data from small animal experiments suggest an additive effect of Xenon when combined with MTH that is bigger than the neuroprotective properties of any of these interventions alone [25-27].

Interestingly, other compounds such as the volatile anesthetic Isoflurane share some of Xenon's organ protective properties, an observation that might be explained by the fact that both isoflurane and Xenon target the same binding site on the NMDA receptor [28], a voltage-dependent neuronal ion channel. Other noble gases such as Argon have been recently proposed to exert similar neuroprotective properties as Xenon [29, 30], while being much more affordable at the same time.

Further insight into the underlying mechanisms will serve not only to optimize current treatment strategies, but also to find novel targets for supplementary therapeutics that

might augment the efficacy of MTH in the future.

Modes of application

Although the beneficial effects of MTH following cardiac arrest are now well described, there is still controversy on who, how, when and for how long to cool (Please see Table 1 for a comprehensive overview of current MTH treatment guidelines).

When first recommended in 2003 [13], MTH was advocated only for unconscious adult patients with return of spontaneous circulation (ROSC) after out-of-hospital cardiac arrest (OHCA), when the initial rhythm was ventricular fibrillation. Since then, a number of studies with historic controls also reported a beneficial effect of MTH in patients with any arrest rhythm [31-35]. Hence, current recommendations now suggest to consider induced hypothermia for comatose adult patients with ROSC after in-hospital cardiac arrest of any initial rhythm, or after OHCA with an initial rhythm of pulseless electric activity or asystole [36] and for children who remain comatose after resuscitation from cardiac arrest [37], although there are no randomized

Table 1: Current standards for post-arrest application of MTH (modified after [67])

Who?	Comatose survivors of OHCA with any initial rhythm
Contraindications	Trauma, severe bleedings Terminal disease Severe coagulopathy
How to induce?	Infusion of cold (4°C) balanced salt solutions (30ml/kg) Ice-Packs
Supportive therapy	Continuous temperature measurement Anesthesia Muscle relaxation Anticonvulsive therapy Blood chemistry: Glucose, electrolytes, coagulation
Target temperature	33±1°C for 24h
Rewarming	Not exceeding 0.5°C per hour Controlled normothermia (37±0.5°C) for 72h post CA

studies in the pediatric population on the effect of therapeutic hypothermia. However, shortly after the publication of the 2010 guidelines a large registry study failed to observe a positive impact on hospital discharge rates in patients with nonshockable rhythm [38]. The disparity of these findings may be explained by the different populations investigated. In contrast to the study by Dumas and colleagues [38] the HACA trial [7] did investigate only a highly selected group of patients with cardiac arrest due to ventricular fibrillation, which per se carry a much better prognosis than patients with other underlying causes of CA [39, 40]. The degree of ischemic sequelae may have obscured possible beneficial effects of MTH in these patients. These results and considerations will certainly impact further development of upcoming guidelines to help selecting the appropriate postarrest therapy for the right group of patients.

Although therapeutic hypothermia has impressively demonstrated its efficacy in animal experiments and clinical trials, the optimal target temperature for post-resuscitation care is still not known. A clinical trial is currently facing this unmet challenge (ClinicalTrials.gov Identifier: NCT01020916). Another controversy during the wake of the introduction of MTH into guidelines in 2005 was the discussion on whether intravascular cooling devices are superior to surface cooling using simple measures such as icebags or cooling blankets (Please see table 2 for a comparison). While the intravascular devices do have their benefits with regard to maintaining target temperature over time [41], they come with certain disadvantages due to their invasiveness and higher costs [42]. Time until reaching target temperature, now considered to be one of the most crucial parameters in MTH therapy, is shorter using conventional surface cooling techniques [41], in part due to the amount of time needed to introduce

Table 2: Surface vs. invasive cooling (modified after [67])

Surface cooling	Invasive cooling
Advantages	
Simple	Self adjusting to target temperature
Preclinical and Clinical application	Reduced nursing time after initial setup
Cheap	
Non-invasive	
Rapid induction characteristics	
Quick setup	
Widely available	
Disadvantages	
Not self-maintaining target temperature	Only available during ICU treatment
Increases nursing time during all periods of cooling	Expensive machines and single use components
Uncontrolled rewarming	Potential infection/dissection hazard
	Slow induction characteristics
	Delayed setup
	Not mobile (interruption during transports)
	No evidence for better neurological outcome

catheters and set up the machines. Furthermore does the more precise cooling with intravascular devices not seem to be associated with a better neurological outcome or long-term survival [43]. In addition, infusion of cold saline may at least match the effectiveness of catheter based approaches for the rapid induction of MTH [44]. The efficacy of infusion-based MTH appears to be independent of the used solution (Saline, Ringer's lactate or combined) [45-47]. While this treatment may even enhance rheological and hemodynamic parameters, caution must be taken in patients with impaired cardiac function, as the infusion of large volumes over a brief period of time may lead to adverse effects such as cardiac failure or pulmonary edema.

Surface cooling appears to be the standard of care in maintaining MTH over time. While this may be easily achieved using ice-water filled bags, technical solutions using blankets with circulating cooling fluids or air are proposed by the industry to reduce nursing time and enhance safety as well as stabilizing target temperature. Fluid based systems offer rapid cooling characteristics of 1.0-1.5°C per hour, and may therefore be used for induction of MTH, while air-based blankets may only be used for maintaining core temperature over time [48]. An alternative approach to MTH treatment in patients after cardiac arrest is the idea that one should rather cool the target tissue than the whole organism in order to maximize efficacy and reduce undesired side effects. These considerations prompted the concept of targeted head cooling, which has been proven to gain similar or better effectiveness as whole body cooling in animal experiments [49-51], offering the appealing option of starting therapeutic hypothermia treatment not with a delay until intensive care treatment is available, but as early as resuscitation efforts are attempted. This concept of targeted cooling led to the development of an intranasal cooling device [52-54] that can be applied by non-physician emergency medical personnel during resuscitation efforts. The advantages of an intranasal application are the close prox-

imity of the nasal cavity to cerebral structures, its well perfused vascular bed, and the lack of hindering or preventing other resuscitation measures such as orotracheal intubation [52]. The evaporating perfluorocarbon cools cerebral structures during cardiac arrest by direct conduction. When circulation is reestablished, brain and body are cooled through indirect convection as the cooled bloodstream removes heat from the organism. A recent study published in 2011 showed that this device is able to provide significant faster regional and systemic cooling as compared to conventional surface cooling [55]. Yet, this novel approach still has to prove whether shifting cooling into the pre-hospital setting and accelerating the cooling process will translate into better ROSC and long-term neurological outcome parameters. Furthermore, does an isolated cerebral cooling approach possibly preclude the treated individual from possible beneficial side-effects on the organism, for instance on cardiac function in survivors of cardiac arrest. Mounting evidence suggests a cardioprotective effect of MTH, that appears to be mediated via Akt- and ERK-pathways [56, 57]. However, there is very limited data on this effect in humans.

There are conflicting results for the duration for which survivors of cardiac arrest should be cooled. In the 2010 guidelines, a period of at least 12h or even more than 24h was proposed, as most studies had been conducted with either of these timeframes [58]. Some investigators report improved outcomes when MTH was extended to periods above 24 hours [59]. However, new data from animal studies suggest that shorter, but rapidly induced periods of hypothermia might be as or even more effective than prolonged treatment with MTH [60]. It remains to be shown if this holds true when this concept is applied in humans.

Adverse effects of hypothermia

Hypothermia has a significant impact on general physiological processes in the organism. The degree of adverse effects however, appears to tightly correlate with the degree of lowering the core temperature.

The foremost obvious side-effect of cooling is shivering as a physiologic response of the body to low temperatures. However, this muscle activity increases the total oxygen consumption and may slow down or prevent sufficient cooling [61]. Therefore, muscle relaxing drugs are widely used to prevent shivering [7, 8], although there is no evidence that muscle relaxation is required for successful application of hypothermia. A combination of Clonidine and Magnesium may be as effective as muscle relaxants to prevent shivering [62], with the advantage that this regimen may not mask potential seizures during MTH treatment. However, this approach requires further investigation before final conclusions can be drawn.

MTH may play a dual role in infections. First it may mask clinical signs of an infection such as rising body temperature; second, it may impair the immune response to an acquired infection. Although several studies suggested at least a trend towards more infections in MTH treated patients [7, 63, 64], the clinical implications are less clear. The benefits of MTH in terms of survival and neurocognitive outcome may in any case outweigh the observed effects on infection/sepsis rates.

MTH induced alterations of electrolyte levels strongly correlate with the depth of hypothermia, and are generally well tolerated in post CA patients [45]. Effects on coagulation correlate well with the degree of cooling and do not appear to add additional bleeding complications [65].

While temperatures around 33°C seem to be safe in terms of onset of cardiac arrhythmias, these may anyhow be more pronounced with temperatures below 30°C [45]. Therefore, caution must be taken to avoid cooling beyond target temperature. In con-

trast to the adverse effects on cardiac rhythm, MTH may even have a positive effect on cardiac contractility [66].

For pharmacotherapy in survivors of cardiac arrest undergoing MTH therapy, it is important to keep in mind that hypothermia unspecifically lowers enzyme activity, which may lead to higher plasma levels of drugs. It must be considered that the activity of enzymes such as Cytochrome P-450 is reduced by 7-20% per 1°C, leading to longer half-lives of circulating drugs, especially sedatives or anesthetics.

When taking care of MTH patients, the clinician should also expect profound effects of MTH on the endocrine systems. These may include an increased insuline resistance, requiring a tight observation of blood glucose levels, as well as Vasopressin (ADH) inhibition with increased diuresis and consecutive hypovolemia [45].

Conclusions

Preserving the brain from ischemia-reperfusion injury is the key challenge of resuscitation research and -care today. While many mechanistic aspects of MTH remain elusive, ongoing research with the aim to optimize target population, mode of application, duration and timing of MTH helps to understand the optimal therapy better and better. Optimized protocols may help more patients survive until hospital discharge, and finally profit in terms of a better neurocognitive outcome and long-term quality of life in the future. Until then, MTH induced as soon as possible after ROSC using surface cooling techniques for 12 to 24h at 33±1°C remains the gold standard in brain resuscitation, eventually expanded by novel technical devices for prehospital targeted cooling of the brain in the near future. Several promising medical gases may expand the neuroprotective care portfolio after ROSC, probably posing as the next leap forward in CPR and brain resuscitation.

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