Review Article

Therapeutic hypothermia after cardiac arrest—Part 1: Mechanism of action, techniques of cooling, and adverse events

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ARTICLE INFO

Article history:
Received 8 March 2012
Received in revised form
17 May 2012
Accepted 19 May 2012
Available online 28 May 2012

Keywords:
Cardiac arrest
Mild-therapeutic hypothermia
Cooling technique

ABSTRACT

MTH is an effective neuroprotective therapy in patients after cardiac arrest. Therapeutic hypothermia is recommended as a standard resuscitation care in such patients with VF/VT as initial rhythm. MTH is easy to perform and without severe side-effects or complications associated with mortality. The goal of the first part of review concentrating on MTH is to describe the mechanism of action, tools for cooling, and adverse events related to this therapeutic technique after the cardiac arrest.

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http://dx.doi.org/10.1016/j.crvasa.2012.05.006
1. Introduction

The incidence of cardiac arrest in Europe is estimated between 0.4–1 per 100 inhabitants per year, which counts between 350 000–700 000 people affected [1]. After the publication of two landmark studies [2,3] in 2002, mild therapeutic hypothermia (MTH) began to be used increasingly in post-resuscitation care. In the same year, the Advanced Life Support Task Force of the International Liaison Committee on Resuscitation stated in their recommendations that unconscious adult patients with spontaneous circulation after an out-of hospital cardiac arrest (OHCA) should be cooled to 32–34 °C for 12 h to 24 h when the initial rhythm was ventricular fibrillation (VF) [4]. In 2005, The American Heart Association incorporated MTH into its advanced cardiac life support guidelines as the late link of the chain of survival [5]. The International Liaison Committee on Resuscitation strongly suggests MTH for comatose survivors after cardiac arrest in their last Recommendation published in 2010 [6]. Recent consensus document from five international critical care societies have made the same recommendation [7]. MTH is also recommended by Czech profession societies [8].

The goal of the first part of review concentrating on MTH is to describe the mechanism of action, tools for cooling, and adverse events related to this therapeutic technique after the cardiac arrest Table 1.

2. History of therapeutic hypothermia

The therapeutic use of hypothermia has a long history. In antiquity, Hippocrates already saved wounded soldiers in snow and ice. In the Napoleonic time the surgeon Dominique Jean Larrey noted that officers who were kept closer to the fire survived less often than soldiers who slept away from fire. The first study dealing with therapeutic hypothermia in patients with severe head injury was published in 1945 [9]. The use of therapeutic hypothermia after cardiac arrest in humans was described in 1950s, but with uncertain benefits [10,11]. The use of MTH as a tool to reduce cerebral oxygen demand and to improve neurological outcomes after cardiac arrest was supported by studies in dogs [12–14]. After 1998, the interest in MTH increased and first clinical studies in humans after cardiac arrest were realized and published [15,16].

3. Mechanism of action

MTH is nowadays one of the most important methods of neuroprotection. Understanding the mechanisms of action, through which MTH provides neuroprotection, will allow a

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**Table 1 – Randomized controlled trials of mild therapeutic hypothermia after cardiac arrest.**

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Cooling mechanism</th>
<th>Initial rhythm</th>
<th>Target temperature</th>
<th>Survival (hypothermia vs. control)</th>
<th>Favourable neurological outcome (hypothermia vs. control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HACA study group [2]</td>
<td>136 vs. 137</td>
<td>External</td>
<td>VF/VT</td>
<td>32–34 °C for 24 h</td>
<td>59% vs. 45% at 6 months p=0.02</td>
<td>CPC 1-2</td>
</tr>
<tr>
<td>Bernard [3]</td>
<td>43 vs. 34</td>
<td>External</td>
<td>VF</td>
<td>33 °C for 12 h</td>
<td>49% vs. 32% at discharge ns.</td>
<td>CPC1-2</td>
</tr>
<tr>
<td>Kim [36]</td>
<td>63 vs. 62</td>
<td>Cold intravenous</td>
<td>All rhythm</td>
<td>33 °C for 24 h</td>
<td>33% vs. 29% at discharge ns.</td>
<td>49% vs 26% at discharge p=0.046</td>
</tr>
<tr>
<td>Castren PRINCE trial [37]</td>
<td>93 vs. 101</td>
<td>Intra-nasal cooling system</td>
<td>All rhythm</td>
<td>Unknown</td>
<td>44% vs .31% at discharge ns.</td>
<td>34% vs 21% at discharge ns.</td>
</tr>
<tr>
<td></td>
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</tr>
</tbody>
</table>

VF—ventricular fibrillation, VT—ventricular tachycardia, CPC—cerebral performance categories, CPR—cardiopulmonary resuscitation.

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**Fig. 1 – Mechanism by which cerebral ischemia causes neuronal damage. (ATP—adenosine triphosphate, TNF-α—tumor necrosis factor-α, IL-1—interleukin 1).**

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better understanding about the indications for this therapy (Fig. 1).

After the cardiac arrest, level of oxygen decreases and an
ischemic cascade takes place. The permanent damage of
neuronal cells occurs after 5 min to 10 min of complete blood
flow cessation [17].

During the ischemia-reperfusion time the reduction in
high-energy molecules, such as adenosine triphosphate (ATP), takes place. The consequence of this decrease leads to
a change in metabolism from aerobic to anaerobic. Anaer-
obic glycolysis increases intracellular phosphate, lactate and
hydrogen ions levels, resulting in intra- and extra-cellular
acidosis. The acidosis increases the inflow of calcium to the
cell. The acidosis and high calcium levels also stimulate the
cell apoptosis and cause cell death [18].

The concentration of intracellular calcium increases [19]
Calcium enters the cell through voltage-sensitive calcium
channels and agonist-operated calcium channels [20]. There
is a dysfunction of sodium/potassium ATP-dependent pump
and ATP-dependent channels, such as calcium, sodium, and
potassium channels. This limits the calcium output from the
cell and the levels of intracellular calcium further increase.
The calcium inflow leads to cell membranes depolarization
and extracellular release of excitatory neurotransmitters
such as glutamate, activating kainite/quisqualate and
N-methyl-D-aspartate receptors persistently [21]. The activa-
tion of these receptors leads to an influx of sodium and
chloride into the cell, causing intracellular hyperosmolarity.
The high osmolarity is followed by an influx of water into the
cell, resulting in intracellular edema and neuronal death [22].

Ischemia with subsequent reperfusion generates large
amounts of free radicals such as hydrogen peroxide, super
oxide and peroxynitrite. These molecules cause cell mem-
branes peroxidation and play an important role in brain
damage after ischemia [23]. There is also an increased
production of pro-inflammatory mediators such as tumor
necrosis factor—α and interleukin 1 [24].

MTH reduces cerebral metabolic rate for oxygen by 6%–10% for
every 1 °C temperature reduction [25]. Hypothermia is
likely to lower lactate levels and other wastes from anaerobic
metabolism decreasing cellular acidosis [26]. Hypothermia
significantly reduces extracellular levels of excitatory neuro-
transmitters, including dopamine and glutamate [27]. The
release of these neurotransmitters is temperature dependent
[28]. The production of free radicals is associated with
oxidative damage that is minimized at lower temperatures
[29]. Hypothermia also delays the induction of pro-inflam-
atory cytokines in human peripheral blood [30].

4. Initiation, duration of MTH, and cooling
techniques

4.1. Initiation

MTH may be divided into three parts: induction, maintenance
and re-warming. The impact of timing of initiation of MTH in
patients after cardiac arrest remains unclear. Experimental
data suggest that MTH should be initiated as soon as possible
[31–33]. However, the initiation of MTH in pre-hospital setting
did not have any impact on neurological outcome in patients
[34]. Two prospective clinical trials in which hypothermia was
achieved within 2 h [3] or at a median of 8 h (interquartile
range 4–16 h) [2] after return of spontaneous circulation (ROSC) demonstrated better outcomes in the hypothermia-
treated than the normothermia-treated subjects.

Pre-hospital versus in-hospital cooling has been studied in
randomized control trial performed by Bernard at al. [35].
Patients with VF as initial rhythm after the ROSC (n=234)
have been included. The studied arm received two liters of
ice-cold Ringer’s solution from paramedics whilst the other
arm received cooling after arrival to the hospital using the
same method. No significant difference was observed in
favorable neurological outcome at discharge between the
two study arms (47.5% in the pre-hospital cooled group and
52.6% in the hospital-cooled group, respectively). In the study
from Kim et al. [36], 63 patients were randomized to receive
an infusion of 0.5 L to 2.0 L of 4 °C normal saline before
hospital arrival, 62 patients were left without intravenous
cooling during the pre-hospital care. In-field cooling was not
associated with increased complications, such as pulmonary
edema. There was no significant difference in survival
between the two groups. This study was limited by short
transport times and missing temperature data.

Castrén at al. studied the intra-arrest cooling. The OHCA
survivors were randomized to receive either trans-nasal
cooling (93 patients) or standard care (101 patients) during
cardiopulmonary resuscitation. After the ROSC, trans-nasal
cooling continued in the studied group, in the second group
MTH was initiated after hospital admission and continued for
24 h. Time to target temperature of 34 °C was shorter in the
treatment group for tympanic temperature (102 min in the
trans-nasally cooled group versus 282 min in control group,
respectively, p=0.03) not for core temperature (155 versus
284 min, p=0.13). Moreover, neurological outcomes (cerebral
performance categories (CPC) scale 1 to 2 at discharge: 34% in
the trans-nasally cooled group and 21% in the control group,
respectively) and overall survival rates (44% versus 31%) were
similar in both groups [37].

4.2. Duration

The optimal duration of cooling must not be shorter than
12 h, and may last up to 24 h. Hypothermia was maintained
with VF. Moreover, most of the clinical trials maintained the
MTH for 24 h. Longer duration of MTH has not been studied
in adults, but hypothermia for up to 72 h has been used safely
in newborns [38].

4.3. Re-warming

Re-warming can be achieved with the same external or
internal temperature control devices used for cooling. It
usually starts after 24 h of MTH. There is no consensus about
the rate of re-warming, but it should be no greater than
0.25–0.5 °C per hour [39]. After the re-warming, hyperthermia
should be actively avoided. MTH may lead to an increased
concentration of sedative drugs because their clearance is
4.4. Cooling techniques

Invasive and non-invasive cooling methods are available for the use in OHCA patients. Intravenous infusion of ice-cold (4 °C) fluids (up to 30 ml kg⁻¹ of saline 0.9% or Ringer’s lactate solution) has been shown to adequately induce MTH and is easy to use in the pre-hospital setting [41,42]. Could fluid infusion alone is not sufficient to maintain MTH [43]. The same effect in inducing and maintaining of MTH have ice packs placed in the groins, armpits and around the head and neck or use of wet towels and fanning. Ice packs are inexpensive and easy to use but have no temperature feedback control and may cause subject over-cooling. Other external surface cooling methods include cooling blankets or fluid pads. It depends on external energy support and is therefore less portable. On the other hand, they operate with a continuous temperature feedback control. The usual cooling rate is up to 1.2 °C per hour [44]. Cooling by peritoneal, pleural or bladder lavage is possible but not generally used. The endovascular cooling system consists of an endovascular catheter containing circulating fluid. It can achieve the cooling rate of 1.5–4.5 °C. For the insertion of the catheter a large vein is needed with its possible thrombo-embolic or infectious complications.

An alternative to whole body cooling is brain hypothermia. Using cranial cap devise placed around the head and neck can be easily achieved the tympanic temperature of 34 °C in 60 min. The Pre ROSC Intranasal Cooling Effectiveness (PRINCE) trial demonstrated safety and efficacy of nasopharyngeal cooling. This device delivers perfluorocarbon aerosol via a catheter into the nasopharynx and provides preferential brain cooling [37].

Tomte et al. [45] compared intravascular and surface cooling techniques in comatose cardiac arrest survivors in a non-randomized study. One hundred sixty seven consecutive patients were included in the study during the five-year recruitment period. There was no significant difference in survival with good neurologic function, either to hospital discharge (38% in surface-cooled group and 45% in intravascular-cooled group, respectively) or at 6-month follow-up (39% versus 45%). Time from cardiac arrest to achieve MTH was equal for both devices (surface-cooled group median 273 min., inter-quartile range 158–330 min. and intravascular-cooled group 270 min., inter-quartile range 190–360 min.).

The patient’s core temperature is most commonly monitored with a probe in the esophagus, bladder, rectum, pulmonary artery or by tympanic temperature measurements [46]. During the cooling, patients are sedated generally by the use of opioids and benzodiazepines. To eliminate the natural body response to decrease in core temperature – shivering – neuromuscular blockers are used.

In our coronary care units, we use ice-cold Saline solution (30 ml per kilogram during the first 30 min) during the coronary angiography or after the admission. Subsequently, we apply refrigerated cooling packs around the head, neck, trunk and groins in the combination with wet towels and fanning (Fig. 2). Before the induction of MTH patients are sedated using midazolam and fentanyl. To prevent shivering, paralysis is induced by intravenous administration of pancuronium as a bolus that is repeated every 4 h. The temperature is controlled by bladder catheter continuously. MTH is maintained for 24 h. Patients are re-warmed passively, with the re-warming rate of 0.5 °C per hour. Sedation is discontinued after the core body temperature of 36 °C is reached. During the next 72 h, we maintain core body temperature between normal ranges. Hyperthermia is actively treated by administration of metamizolum.

5. Adverse effects

The most often reported adverse effects of MTH include hypokalemia, hypomagnesemia, hypocalcaemia, arrhythmias, hypotension, seizure, hyperglycemia, coagulopathy and increased incidence of pneumonia and sepsis. Hypokalemia induced by MTH is caused by the influx of potassium into the cells and increased diuresis. Regular checks of mineralogram are necessary during MTH. On the other hand, aggressive supplementation of potassium during MTH may result in hyperkalemia during re-warming [47]. MTH reduces insulin sensitivity and insulin secretion. Both of these may lead to hyperglycemia [48]. Enzymes taking part in coagulations have lower activity with hypothermia. Bleeding must be watched for and if occurs, interruption of MTH is indicated. Some authors reported the
Only sustained hyperglycemia (odds ratio 2.3, 95% CI 1.6–3.6, \( p < 0.001 \)) and seizures treated with anticonvulsants (odds ratio 1.0, 95% CI 0.46–2.2, \( p = 0.91 \), and odds ratio 0.30, 95% CI 0.12–0.79, \( p = 0.01 \), respectively) were associated with an increase in clinically significant arrhythmias during MTH [49]. Controversially, in the randomized trial published by Tiainen et al. [50] the use of MTH of 33°C for 24 h after cardiac arrest was not associated with an increase in clinically significant arrhythmias [51].

![Image](54x340)

**Fig. 3 – Hypothermia flow chart (modified by Delhaye et al. [52])**.

In the prospective, observational, registry-based study performed in 22 hospitals in Europe and United States the association between adverse events recorded during critical care and mortality in out-of-hospital cardiac arrest patients \( (n=765) \) treated with therapeutic hypothermia was studied. Only sustained hyperglycemia (odds ratio 2.3, 95% CI 1.6–3.6, \( p < 0.001 )\) and seizures treated with anticonvulsants (odds ratio 4.8, 95% CI 2.9–8.1, \( p < 0.001 \) ) were associated with increased mortality in a multivariate model. An increased frequency of bleeding and sepsis occurred after invasive procedures (coronary angiography, intravascular devices for cooling, intra-aortic balloon pump), but bleeding and sepsis were not independently associated with increased mortality (odds ratio 1.0, 95% CI 0.46–2.2, \( p = 0.91 \), and odds ratio 0.30, 95% CI 0.12–0.79, \( p = 0.01 \), respectively) [51].

### 6. Conclusion

MTH is an effective neuroprotective therapy in patients after cardiac arrest. Therapeutic hypothermia is recommended as a standard resuscitation care in patients after cardiac arrest. MTH is easy to perform and without severe side-effects or complications associated with mortality. MTH should be initiated as soon as possible. Finally, at this time, we recommend the use of MTH in all cardiac arrest survivors irrespective of initial rhythm who remain unconscious after ROSC to increase the chance of brain recovery after the ischemic-reperfusion injury. The optimal duration and target temperature will be hopefully known after the results of ongoing trials.

### References


