Review Article

Therapeutic hypothermia after cardiac arrest—Part 2
Evidence from randomized, observational trials

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ABSTRACT

MTH is now part of post-resuscitation care after a witnessed cardiac arrest due to VF/VT, and offers evidence of improved neurological outcomes and survival. The evidence of MTH benefits in patients with non-shockable rhythms is less certain. The second part of this review is dedicated to MTH, which focuses on randomized and non-randomized clinical trials, as well as observational registries that have studied the efficacy of MTH following cardiac arrest in different patient populations

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1. Introduction

The majority of patients who survive out-of-hospital cardiac arrest (OHCA) usually develop some degree of neurological disability caused by ischemia-reperfusion cerebral injury [1]. Favorable outcomes in patients admitted to hospitals after a successful return of spontaneous circulation (ROSC) following a OHCA, range from 11% to 48% [2].
Some clinical trials have tried to demonstrate beneficial effects of drugs such as barbiturates [3], magnesium, steroids [4] and calcium-channel antagonists [5] in reducing neurological impairment in patients after cardiac arrest. Unfortunately, the results of these studies showed no benefit from these drugs. With the administration of mild therapeutic hypothermia (MTH) following resuscitation after cardiac arrest, we see for the first time, that the neurological recovery of these patients has improved, and mortality has decreased.

The second part of this review is dedicated to MTH, which focuses on randomized and non-randomized clinical trials, as well as observational registries that have studied the efficacy of MTH following cardiac arrest in different patient populations.

2. Cardiac Arrest due to Ventricular Fibrillation/Pulseless Ventricular Tachycardia

In 2002, two prospective randomized clinical studies [6,7] were published which compared the outcomes in comatose survivors after OHCA with, or without, hypothermia. One of these studies [6] was organized in conjunction with nine centers in five European countries. A total of 3551 patients were assessed as eligible for the trial and 275 patients were enrolled. The inclusion criteria were: witnessed cardiac arrest, ventricular fibrillation/ pulseless ventricular tachycardia (VF/VT), time intervals of 5 to 15 min from collapse to resuscitation, and a time interval of no more than 60 min from collapse to ROSC. Exclusion criteria were: a tympanic-membrane temperature below 30 °C on admission, pregnancy, response to verbal commands after ROSC, a mean arterial pressure of less than 60 mmHg for more than 30 min following ROSC, evidence of hypoxemia longer than 15 min after ROSC, terminal illness, and preexisting coagulopathy. All patients received standard intensive care. Sedation was induced using midazolam and fentanyl. Shivering paralysis was induced by intravenous administration of pancuronium. Temperature measurements were made using a bladder temperature probe. Patients randomly assigned to the group with hypothermia were cooled to a target temperature of 32 °C to 34 °C for 24 h with the use of an external cooling device. If the goal temperature was not achieved within 4 h after ROSC, ice packs were applied. Passive re-warming took 8 h. The primary outcome was a favorable neurological outcome within 6 months, defined as either a Pittsburgh Cerebral-Performance Category (CPC) 1 (good recovery) or 2 (moderate disability). Secondary end points were overall mortality at 6 months and the rate of complications during the first 7 day following cardiac arrest. Bleeding of any severity, pneumonia, sepsis, pancreatitis, renal failure, pulmonary edema, seizures, arrhythmias and blood pressure were also recorded.

In this trial, 137 patients were randomly assigned to the MTH group, and 138 to the group without MTH (w/o MTH). At six months, a favorable neurological outcome was reached in 55% of patients in the group with MTH, compared with 39% of patients in the group w/o MTH (p = 0.009). To prevent one unfavorable neurologic outcome, 6 patients needed to be treated with MTH. Six months after cardiac arrest, death occurred in 41% of patients in the group with MTH and 55% of patients in the group without (p = 0.02). The rates of complications did not differ significantly between the two groups (70% MTH vs. 73% w/o MTH).

The second study [7] was performed in Melbourne, Australia between 1996 and 1999. In this pseudo-randomized trial, patients, after cardiac arrest with ROSC, were randomly assigned either to the MTH group, or the group w/o MTH, (assignment was based on the day of the month). Inclusion criteria were cardiac arrest due to VF/VT, ROSC, and persistent coma after ROSC. Patients were excluded if younger than 18 years (for men) and younger than 50 (for women, due to the possibility of pregnancy), cardiogenic shock, and coma caused by something other than cardiac arrest. Core body temperature was monitored via either the tympanic membrane or the urinary bladder, until a pulmonary-artery catheter was placed. The initial basic cooling was administered in the ambulance. On hospital arrival MTH was continued using cold packs on the head, neck, torso and limbs; the target pulmonary artery temperature was 33 °C, which was maintained for 12 h following hospital admission. During cooling, patients were sedated and paralyzed with midazolam and vecuronium. Beginning at 18 h, patients were actively re-warmed for the next 6 h by an external warming device. The primary outcome was survival to hospital discharge, with sufficiently good neurological function to be sent either home or to a rehabilitation facility. The secondary outcomes included the hemodynamic, biochemical and hematologic effects of hypothermia.

From a total of 77 patients, 43 were assigned to hypothermia and 34 to normothermia. A favorable neurological outcome occurred nearly twice as often in the group with MTH (49% of patients) as opposed to the control group (26% of patients, p = 0.046). The difference in mortality rates between the two groups did not reach the level of significance (51% vs. 68%).

Both of these studies investigated the effects of MTH in patients with ROSC after cardiac arrest when VF was the initial rhythm. Major limitations were: (a) the inclusion of a highly select group of patients (based on inclusion/exclusion criteria, 92% of patients were excluded), (b) physicians were not blinded to the treatment arm, (c) core temperatures in the control group were higher than the normal upper range in the population.

3. Cardiac Arrest due to Asystole/Pulseless Electrical Activity (PEA).

Unlike the evidence in patients where the first documented rhythm was VF/VT, there is a lack of published data in cardiac arrest survivors where the initial rhythm was asystole/PEA (non-shockable rhythm).

Hachimi-Indrissi [8] conducted a feasibility study in which he investigated the use of MTH in patients with cardiac arrest due to asystole/PEA and who remained unconscious after ROSC. In the hypothermia group, a helmet-like device was placed around the head and neck in order to induce MTH with a target temperature of 34 °C for a maximum of 4 h. No additional devices were used to reduce body temperature.
Table 1 – Nonrandomized studies of cardiac arrest survivors with a non-shockable initial rhythm.

<table>
<thead>
<tr>
<th>Author</th>
<th>Study type</th>
<th>Method of cooling</th>
<th>Target temperature</th>
<th>Duration of cooling</th>
<th>Survival (hypothermia vs. control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Don[21]</td>
<td>Retrospective/historical control subjects</td>
<td>External</td>
<td>32 °C–34 °C</td>
<td>24 h</td>
<td>21% vs. 19%, p = ns</td>
</tr>
<tr>
<td>Oddo[22]</td>
<td>Retrospective</td>
<td>External</td>
<td>33 °C</td>
<td>24 h</td>
<td>17% vs. 9%, p = ns</td>
</tr>
<tr>
<td>Arrich[23]</td>
<td>Prospective</td>
<td>Endovascular</td>
<td>33 °C</td>
<td>24 h</td>
<td>35% vs. 19%, p = 0.02</td>
</tr>
<tr>
<td>Testori[2]</td>
<td>Retrospective</td>
<td>External or endovascular or combination</td>
<td>32 °C–34 °C</td>
<td>24 h</td>
<td>61% vs. 75%, p = 0.025</td>
</tr>
<tr>
<td>Lundbye[24]</td>
<td>Prospective/historical control group</td>
<td>Endovascular</td>
<td>32 °C–34 °C</td>
<td>18 h</td>
<td>38% vs. 19%, p = 0.03</td>
</tr>
</tbody>
</table>

consecutive patients were included in the study over a 6-month period. 16 patients were randomly delegated to the MTH group and 14 patients were placed in the control group. The first documented rhythm was asystole in 80% of patients, and PEA in the remaining 20%. The mortality rate was high in both patient populations; 81% in the MTH group and 92.8% in the control group. The authors concluded that MTH induced using a helmet-like device was feasible, easy to perform, inexpensive and effective, with no increase in complications. This study was not able to show a significant advantage in terms of either the neurological or overall outcomes of treatment with MTH.

In a study from Kim et al. [9], 125 patients after OHCA (irrespective of post-arrest ECG) were randomized to cooling in the field before their arrival to the emergency department or to standard resuscitation care. In the MTH group (63 patients), up to 2 l of 4 °C normal saline infusion was administered during transport. There was a trend toward improved survival to discharge in patients randomized to field cooling when the initial rhythm was VF. The reverse was observed when the initial rhythm was not VF. However, none of these differences were statistically significant.

Observational studies in non-shockable OHCA patients provided conflicting results (Table 1). Dumas et al. [10] described the prognostic value of MTH in neurological outcomes at hospital discharge, based with the first-recorded rhythm, in a large cohort of 1145 patients. Hypothermia was started on ICU admission, by means of an external cooling device, and was used during the first 24 h in order to obtain a target temperature between 32 °C and 34 °C. Over the course of the study, therapeutic hypothermia was induced in 65% of patients with VF/VT, and 60% of patients with asystole/PEA. A good neurological outcome, defined as a CPC 1–2, was observed at hospital discharge in 30% of all patients. Hypothermia was associated with a significantly better outcomes in patients with VF/VT (44% in the group with hypothermia vs. 29% in the group without hypothermia, p < 0.001), but not in patients with asystole/PEA (15% MTH vs. 17% w/o MTH n.s.). Following multivariable analysis, hypothermia tended to be inversely associated with a good outcome (adjusted OR 0.71, 95% CI 0.37–1.36, p = 0.3) in the asystole/PEA subgroup.

In their meta-analysis of two randomized trials and twelve non-randomized trials, Kim et al. [11] investigated the effects of MTH on the survival or neurological outcomes in adult cardiac arrest survivors with non-shockable initial rhythms. They analyzed randomized and non-randomized studies separately. The two randomized trials included only 44 subjects and were inconclusive regarding the effects of MTH on patients with non-shockable initial rhythms. The non-randomized studies included survival data for 390 subjects and neurological outcomes for 289 subjects treated with MTH. The pooled results showed that the MTH group experienced reduced in-hospital mortality in patients resuscitated from cardiac arrest who presented with non-shockable initial rhythms (risk ratio 0.84, 95% CI 0.78–0.92, p < 0.0001). The neurological outcome at hospital discharge had a pooled risk ratio of 0.95 with no statistical difference. However, most of the studies had very low quality evidence.

4. Therapeutic Hypothermia and Coronary Angiography.

The feasibility and safety of percutaneous coronary intervention (PCI) in conjunction with MTH following cardiac arrest was studied by Batista et al. [12]. It was a single center study using a retrospective cohort. A total of 90 adult comatose patients, who presented between 0 and 6-h after cardiac arrest and underwent MTH, were included and reviewed. Patients who were in shock on admission were also included in this study. All patients were cooled to a target temperature of 32 to 34 °C for 24 h. From a total of 90 patients, 30 of them underwent PCI following MTH induction and were compared to 70 patients who underwent MTH without PCI. A favorable neurological outcome at discharge was observed in 30% of patients in the PCI with MTH group, and in 22% of patients in the MTH w/o PCI group (n.s.). The mortality rate was not different between groups (PCI with MTH group 60% vs. MTH w/o PCI 70%, n.s.). There was no increase in adverse events in patients who underwent PCI with MTH compared to patients with MTH w/o PCI (p = 0.054). No significant difference was found in the rates of arrhythmias, infection, coagulopathy or hypotension. Wolfram et al. [13] reported that initiation of MTH did not result in a prolonged door-to-balloon time in patients after cardiac arrest due to acute myocardial infarction. MTH and coronary angiography are now recommended for adult patients less than 75 years of age following cardiac arrest related to VF in the presence of acute coronary syndrome with STE-elevations [14].

Dumas et al. [15] assessed whether or not immediate revascularization could improve the outcome in 435 patients.
admitted to hospital after a cardiac arrest presumed to be of cardiac origin. OHCA patients, in whom ROSC was achieved, were admitted directly to the cardiac catheterization laboratory, regardless of ECG findings. A PCI was performed if either a coronary artery occlusion or an unstable lesion(s) were present. MTH was induced after the procedure. The population was divided into 2 subgroups according to the post-ROSC ECG (ST-segment elevation and other ECG patterns). The primary outcome was hospital survival at discharge. At that time, neurological status was assessed using the CPC score. In the ST-segment elevation group (n = 134), at least 1 significant coronary artery stenosis was found in 96% of patients. PCI was successful in 90% of patients. In the 301 patients with other ECG patterns, 58% had at least one significant coronary stenosis and PCI was performed in 31% of patients. An increased hospital survival rate was present both in patients with ST-segment elevation (54% with PCI and 31% without, or failed, PCI, p < 0.001) and in patients with other ECG patterns (47% with PCI vs. 31% no or failed PCI, p < 0.001) who underwent PCI. Multivariate analysis showed successful PCI to be an independent predictor of survival, regardless of the initial ECG pattern (OR 2.06, 95% CI, 1.16 to 3.66, p < 0.001). Univariate analysis revealed that MTH was associated with a better prognosis (p = 0.006).

In the author’s cardiology department, urgent coronary angiography is performed on all patients where myocardial ischemia is the possible cause of cardiac arrest (i.e., all patients with suspected acute coronary syndrome, patients with left ventricle dysfunction, etc.).

5. Mild Therapeutic Hypothermia and In-hospital Cardiac Arrest (IHCA)

In January 2012, a study from Kory et al. reported results from [16] a retrospective, historical controlled trial of IHCA patients admitted to the Medical Intensive Care Unit before and after implementation of MTH. They assessed its benefit in a select population of IHCA patients matched with historical controls. Between the years 2003 and 2009, they identified 118 patients after an IHCA, which occurred in the Emergency Department or after hospital admission. Patients with terminal illnesses, defined as metastatic cancer, advanced treatment refractory AIDS, class IV heart failure and patients with Do-Not-Resuscitate orders, were not included in the study. All IHCA patients meeting MTH criteria during the 3 year period prior to the implementation of MTH served as the control group; all IHCA patients meeting inclusion criteria who were admitted after the implementation of MTH in 2006 served as the intervention group. The primary outcome was good neurological function (CPC score 1–2). A secondary outcome was best neurological function after completion of MTH but prior to discharge. Patients treated by MTH received continuous sedation with fentanyl and midazolam, and 25 mg bolus of atracurium at the start of cooling. A temperature range of 32–34 °C was maintained for 24 h.

A total of 33 IHCA patients met the inclusion criteria for MTH during the study period. 17 patients formed the MTH group and 16 patients formed the control group. Overall, 71% of patients in the MTH group, and 69% of patients in the control group, died prior to discharge (p = 0.87). A secondary outcome (best neurological function prior to discharge) was achieved in 41% of patients in the MTH group and in 31% of patients in the control group (p = 0.55). Complication rates (bleeding, pneumonia, acute renal failure, pulmonary edema, sepsis) were similar in the two groups.

The main limitation of this study was its small sample size and retrospective nature. The study focused on patients admitted to the Medical Intensive Care Unit (which was not a coronary care unit) and resulted in a population with a majority (91%) of asystole and PEA rhythms. Therefore, the results of this study may not reflect the full impact that MTH can have on IHCA patients with VF/VT rhythms, which deserves further study.

The causes of death after IHCA are different from those after OHCA. Neurological injury is less likely to be the primary cause of death among IHCA patients. Laver [17] reported that 68% of OHCA patients die of neurological injury vs. 23% of IHCA patients. Similarly, deaths due to multi-organ failure occurred in 50% of IHCA, versus 9% of OHCA patients. Outcomes from IHCA are consistently better when the first monitored rhythm is VF/VT, rather than asystole/PEA. Unfortunately, in the majority of studies, VF/VT was the first monitored rhythm in only 20%–35% of IHCA survivors [18].

6. Indications and Contraindications

MTH is indicated in adult OHCA survivors with ROSC within 60 min from the time of collapse, who remain unconscious following ROSC, and whose initial rhythm was VF/VT (class I recommendation, level of evidence B) [19].

Absolute contraindications are: hemorrhagic stroke confirmed by computed tomography, cardiac arrest due to trauma, a Glasgow Coma Scale score of 8 or higher after ROSC, cardiac arrest due to drug overdose, preexisting hypothermia with a temperature <34 °C, uncontrolled active bleeding, uncontrolled hemodynamically unstable arrhythmias, and pregnancy. There are also relative contraindications, such as known coagulopathy and severe hypotension (mean arterial pressure <60 mmHg) not treatable by fluid infusion, vasopressors or invasive hemodynamic support [20].

7. Conclusion

MTH is now part of post-resuscitation care after a witnessed cardiac arrest due to VF/VT, and offers evidence of improved neurological outcomes and survival. The evidence of MTH benefits in patients with non-shockable rhythms is less certain. Induction of MTH does not delay reperfusion in patients with acute coronary syndrome. It has been shown that successful PCI is an independent predictor of survival, regardless of the initial ECG pattern. There are many clinical trials underway and there are expectations that the results will provide a more definitive answer regarding the role of MTH in patients with non-shockable rhythms, optimal temperature management and the optimal duration of MTH.
Acknowledgements

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References