Contemporary practices in postcardiac arrest syndrome: the role of mild therapeutic hypothermia

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***Abstract*:** Out-of-hospital cardiac arrest remains a major cause of mortality and morbidity despite progress in resuscitative practices. The number of survivors with severe neurological impairment at hospital discharge is similarly dismal. Recently, much attention has been directed toward the use of mild therapeutic hypothermia in the care of comatose survivors with postcardiac arrest syndrome. Recent research suggests mild hypothermia lowers mortality and improves neurological outcome after successful treatment of cardiac arrest. The current 2005 updated guidelines of International Liaison Committee on Resuscitation and European Resuscitation Council recommend the utilization of mild induced hypothermia in postresuscitation treatment. Hypothermia induction in order to avoid the pathophysiological mechanisms of euthermia and hyperthermia and subsequent complications are briefly discussed. Cooling methods, potential side effects and questions regarding implementation of therapeutic hypothermia recommendations in every day clinical practice and future investigation are also addressed.

***Keywords*:** cardiac arrest, cardiopulmonary resuscitation, mild therapeutic hypothermia, postcardiac arrest syndrome

Introduction

Out-of-hospital cardiac arrest (CA) affects more than 375,000 individuals per year in Europe [de Vreede-Swagemakers *et al.* 1997], while it carries a greater than 90% mortality rate, leading to over 300,000 deaths in the United States each year [Thom *et al.* 2006]. Despite the development of pharmacologic therapies for CA and the improved access to electrical defibrillation this mortality rate has not declined significantly over the past few decades. Cardiopulmonary resuscitation restores the return of spontaneous circulation (ROSC) in about 100,000 patients a year in the US while 60% of these die from neurological complications [Booth *et al.* 2004].

Post-CA syndrome represents a complex interaction of underlying pathologies including brain injury, myocardial dysfunction, systemic ischemia/reperfusion response, unresolved pathologic process leading to CA and the body's response to hypoxia and hypoperfusion [Nolan *et al.* 2008]. Among the few survivors to hospital discharge, neurological impairment often remains a lasting morbidity. Only 3–20% of resuscitated patients are able to resume their former lifestyles. The means by which hypothermia provides neuroprotection are uncertain, but preliminary studies suggested that mild therapeutic hypothermia (MTH) could improve cardiological and neurological outcome in patients who suffered CA, while MTH side effects could be managed successfully in modern intensive care units (ICUs) [Krause *et al.* 1986].

Therapeutic hypothermia after cardiac arrest

A number of landmark studies and a meta-analysis have demonstrated that cooling patients can provide significant survival benefit after initial resuscitation from CA [Holzer *et al.* 2005b; Bernard *et al.* 2002; HACA Study Group 2002; Hachimi-Idrissi *et al.* 2001]. The European HACA (Hypothermia After Cardiac Arrest) trial group demonstrated an improvement in survival to hospital discharge with favorable neurological status in cooled patients compared with

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normothermic patients surviving arrest (53% *versus* 36%, respectively), with no significant neurological adverse events from cooling [HACA Study Group, 2002]. In the Australian study carried out by Bernard and colleagues, there was a significant difference in the rate of good neurological outcome: 21 of 43 patients (49%) in the hypothermia group *versus* 9 of 34 patients (26%) in the normothermia group [Bernard *et al*. 2002]. In a previous, limited clinical trial by Hachimi-Idrissi and colleagues, improved outcome was reported in 2 of 16 patients randomized to hypothermia of 34°C for a maximum of 4 hours but in none of the 14 patients randomized to normothermia (Table 1) [Hachimi-Idrissi *et al*. 2001]. Several of these MTH investigations were well-designed randomized controlled trials, providing better evidence for the use of cooling than many pharmacologic interventions after CA [Holzer *et al*. 2005b].

On the strength of these studies, the International Liaison Committee on Resuscitation (ILCOR) and the American Heart Association (AHA)/ European Resuscitation Council in the 2005 published guidelines [ECC Committee, Subcommittees and Task Forces of the American Heart Association, 2005; Nolan *et al*. 2005] recommend that:

- unconscious adult patients with ROSC after out-of-hospital CA (ventricular fibrillation [VF]) should be cooled to 32–34°C for 12 hours;
- similar therapy may be beneficial for patients with non-VF arrest, out-of- or in-hospital arrest.

Underlying mechanisms and cooling methods

Various pathophysiological mechanisms are associated with brain damage during and after CA and subsequent resuscitation. A temporary phase of interrupted or limited cerebral blood flow is followed by rapid or delayed cell reperfusion [Froehler and Romergryko, 2007]. Neurological injury and mortality after ROSC may be due in part to this 'ischemia–reperfusion' injury. This is believed to result from interruption of blood flow (ischemia) while unrestrained reperfusion (return of blood flow after resuscitation) may magnify these injury processes [Bouch *et al*. 2008] (Figure 1). Hypothermia may block a number of these steps and minimize cellular damage by slowing cerebral metabolism in relation to other mechanisms [Soar and Nolan, 2007] (Table 2). These include a reduction in neuronal apoptosis, inhibition of chemical reactions associated with reperfusion injury, alterations in intracellular cation concentrations due to ion pump dysfunction, suppression of inflammatory cytokines, reduction of free radical production and reduction of cerebral edema [Böttiger *et al*. 2007]. It appears that cooling as soon as possible (within several hours of resuscitation) is best, although animal work suggests that cooling during resuscitation or within 15 minutes of ROSC, when cooling is maintained for only a short duration (1–2 hours), might be even better. However, this has not yet been shown clinically [Abella *et al*. 2004; Kuboyama *et al*. 1993; Sterz *et al*. 1991]. No differences in neuroprotection were recorded in a rat model of CA when a 24-hour period of cooling was either initiated at the time of ROSC or delayed by 1 hour [Hicks *et al*. 2000]. In contrast, in a gerbil forebrain ischemia model, constant neuroprotection was attained when hypothermia was induced at 1, 6, or 12 hours after reperfusion and preserved for 48 hours, while neuroprotection was impaired when the commencement of therapy was delayed [Colbourne *et al*. 1999]. In another animal (swine) study, extracorporeal venovenous cooling has been tested as a thriving procedure to rapidly induce MTH [Holzer *et al*. 2005a]. There are no studies comparing early *versus* delayed hypothermia in humans.

Infusion of cold (4°C) lactated Ringer solution at 30 ml/kg over 30 minutes after resuscitation from out-of-hospital CA or traditional ice packs placed on the groin and armpits and around the neck and head has been a safe and successful cooling technique [Kim *et al*. 2005]. This method has been sufficient and effective also in prehospital settings, and has also been studied in combination with endovascular cooling or with ice-water cooling blankets [Kliegel *et al*. 2005; Polderman *et al*. 2005]. It has been proposed that for out-of-hospital CAs, victim cooling should be started as soon as possible, ideally at the scene of the arrest by the ambulance crew [Kämäräinen *et al*. 2008; Kim *et al*. 2007].

Numerous internal cooling techniques and external or surface cooling devices (Table 3) alone or in combination with the above measures have been described for inducing mild hypothermia [Angus and Milbrandt, 2006]. These include ice bags, blankets containing circulating coolant

Table 1. Outcomes of mild induced therapeutic hypothermia utilization after out-of-hospital cardiopulmonary resuscitation.

	Hypothermia (%)	Normothermia (%)	RR (%)	*p*-value
Alive at hospital discharge with favorable neurological recovery				
HACA Study Group [2002]	72/136 (53%)	50/137 (36%)	1.5 (1.14–1.89)	0.006
Bernard *et al.* (2002)	21/43 (49%)	9/34 (26%)	1.75 (0.99–2-43)	0.052
Hachimi-Idrissi *et al.* [2001]	4/16 (25%)	1/17 (6%)	4.25 (0.70–53.83)	0.16
Alive at 6 months with favorable neurological recovery				
HACA Study Group [2002]	72/136 (52%)	50/137 (36%)	1.44 (1.11–1.76)	0.009

RR, relative risk.

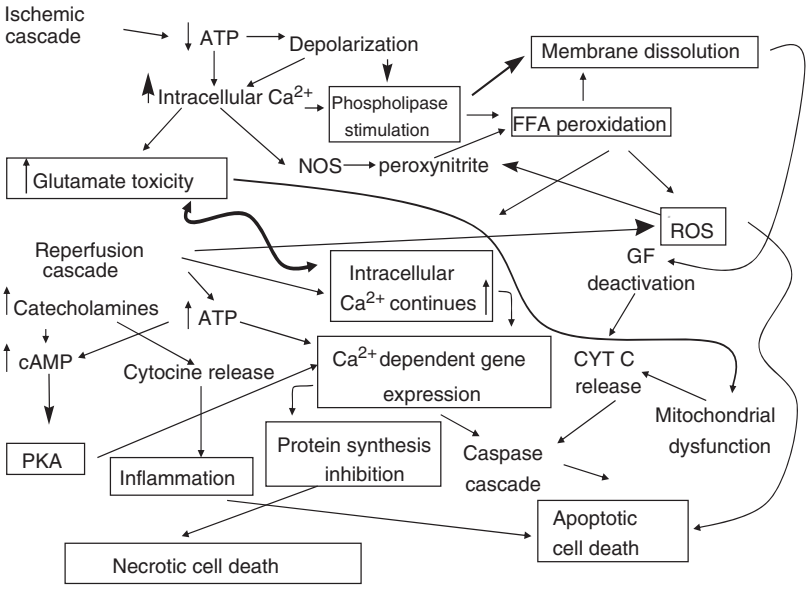

Figure 1. Ischemia through ATP depletion leads to neurilemma depolarization and to inappropriate accumulation of intracellular Ca^{2+}. Elevations of intracellular Ca^{2+} concentration activates various intracellular enzyme systems, including phospholipases causing accumulation of free oxygen radicals, membrane damage and necrotic cell death. Accordingly reperfusion leads to a shift of ATP concentration and activation of protein kinase A which increases the expression of inhibitory proteins through glutamate toxicity and Ca^{2+}-dependent gene expression. Furthermore, in reperfused tissue, reactive oxygen species (ROS) and peroxynitrite, mediated through ischemia mechanisms, in combination with inhibited growth factor signalling amplify their toxic effects to mitochondria. Consequently, the activation of apoptotic caspases initiates pathways of programmed cell death and neuronal apoptosis. PKA, protein kinase A; GF, growth factor; FFA, free fatty acids; ROS, reactive oxygen species; CYT C, cytochrome C; ATP, adenosine triphosphate; c-AMP, cyclic adenosine monophosphate; NOS, nitric oxide synthase.
[Source: Brian, J. and O'Neil, M.D. (2007) Hypothermic resuscitation in patients with CNS injury due to cardiac arrest. In *4th Mediterranean Emergency Medicine Congress, Sorrento, Italy, September 17*].

or cold air, a helmet or cooling cap with chemical cooling capacities, drugs, cold carotid artery infusion, ice-water nasal lavage, cold peritoneal lavage, cardiopulmonary bypass, and endovascular cooling with a catheter [Holzer *et al.* 2006]. The utilization of these simply performed cooling methods has been approved during the transportation of patients to a cardiac catheterization laboratory [Nolan *et al.* 2008]. Close attention should be taken during the cooling and rewarming stages, because metabolic state, plasma electrolyte balance, and hemodynamic conditions may alter instantly. The optimal rate of rewarming has not been defined clinically, but current practice is to rewarm gradually with a rate of 0.25–0.5°C per hour [Sterz *et al.* 2003].

Management and potential adverse effects

Hypothermia deteriorates immune function leading to an approximately 19% rate of infection as opposed to a 6% rate of normothermic patients [HACA Study Group, 2002]. Therefore, it is

Table 2. Mechanisms through which the benefits of mild induced hypothermia offer the maximal neurologic protect for patients with postcardiac arrest syndrome.

Decreased cerebral metabolism: 5–7% for every 1°C
Slowing the ischemic loss of ion gradients
Reduction of calcium influx
Suppression of excitatory amino acid (glutamate) release
Reduction in free radicals, and anti-inflammatory effects ↓ (tumor necrosis factor α, interleukin-1).
Attenuation of blood–brain barrier disruption and ensuing edema that occurs after ischemia
Reduces thermo-pooling effect

Table 3. Cooling techniques and mechanisms of action.

Core cooling		
Method	Basic mechanism	Manufacturer
Intravascular catheters	Conduction	"Celcius Control", "CoolLine" "Coolgard"
Infusion of ice-cold (4°C) Fluids	Conduction	
Extracorporeal circulation	Conduction	Various devices
Antipyretic agents	Effect on central nervous system	Various drugs
Peripheral cooling		
Fans	Convection	
Air-circulating cooling blankets	Convection	"Polar Air" and "Bair Hugger", USA
Ice packs	Conduction	
Water-circulating cooling blankets	Conduction	"Blanketrol II hyper-hypothermia", Cincinnati, USA
Immersion	Conduction	
Specially designed beds	Conduction	"TriaDyne", USA
Cooling caps	Conduction	"Frigicap"
Water and alcohol sprays	Evaporation	
Sponge baths	Evaporation	
Exposure of skin	Radiation	

important that all patients who receive hypothermia should receive optimal ICU care such as frequent turning, oral care every 2–4 hours, ventilator bundling interventions, glucose level control, peptic ulcer prophylaxis, and deep vein thrombosis prophylaxis [Arrich, 2007]. The treatment involves sedation and mechanical ventilation (PO2 90–100 mmHg) with a temperature goal of 32–34°C within 2–6 hours [ECC Committee, Subcommittees and Task Forces of the American Heart Association, 2005]. Temperature monitoring with an esophageal probe, urinary output checking with a bladder catheter, and a mean arterial blood pressure target of 60–80 mmHg are essential, in combination with (a) management of cardiac arrhythmias (usually bradyarrhythmias), (b) pH maintenance within normal range, (c) monitoring for electrolyte disorders and hyperglycemia prevention [Oddo *et al*. 2006]. The most important process is to prevent shivering, which is common, principally during the induction phase, leading to warming and increased oxygen consumption [Bernard *et al*. 2002; HACA Study Group 2002]. Use of sedation and muscle relaxation prevent shivering [ECC Committee, Subcommittees and Task Forces of the American Heart Association, 2005; Holzer *et al*. 2005b]. During endovascular cooling, skin warming with the utilization of forced-air blankets has effectively reduced shivering [Guluma *et al*. 2006]. All of these processes represent a treatment protocol that is not difficult to apply to populations who suffer out-of-hospital CA (Table 4).

Potential and frequent complications (Table 5) of mild-to-moderate hypothermia include coagulopathy and impaired coagulation cascade, electrolyte disorders, increased diuresis, insulin resistance, and changes in drug effects and drug metabolism [Nolan *et al*. 2005]. Clinical evidence suggests that the beneficial effect of amiodarone or lidocaine is abolished during ventricular arrhythmias in the

Table 4. Basic principles of a treatment protocol applying mild therapeutic hypothermia.

Cool early (in the emergency department). Use any cooling method. Treatment can be continued while in the percutaneous coronary intervention laboratory and in the intensive care unit.
Temperature goal 32–34°C within 2–6 hours.
Monitor temperature with esophageal, rectal, or bladder probe, Q1 h
Mean arterial pressure goal 60–80 mmHg, monitoring for life-threatening arrhythmias
Maintain HOB at 30°C elevation for neuroprotection.
No heated humidification on the ventilator
Maintain PO_2 90–100 mmHg
Maintain pH within normal range
Patient comfort and sedation: continuous pharmacologic neuromuscular blockade to prevent shivering
Begin enteric feeding as soon as practical
Passively rewarm (no heating blanket) after 24 hours of cooling has been completed.

HOB, Head of Bed.

Table 5. Potential adverse effects of mild therapeutic hypothermia.

Arrhythmias
Pneumonia
Bleeding
Sepsis
Seizures
Renal failure

Table 6. Contraindications to mild therapeutic hypothermia.

Pregnancy
Severe cardiogenic shock
Primary coagulopathies
Do not resuscitate status
Coma unrelated to cardiac arrest
Received CPR greater than 45 minutes
Cardiac arrest that is not due to primary ventricular fibrillation or ventricular tachycardia (e.g. PEA, asystole, noncardiac, etc.)*

PEA, Pulseless Electrical Activity.

hypothermic heart [Schwarz *et al.* 2003]. Intracellular movements of potassium, magnesium, and phosphate during hypothermia lead to unpredictable changes in the mode of action potential and drug–cardiomyocyte interactions. Of late, animal models researching the impact of hypothermia after rewarming have shown that drug metabolism is successfully normalized [Tortorici *et al.* 2009].

Myocardial ischemia and severe rebound hyperthermia may also occur. Recently, life-threatening recurrence of ventricular fibrillation has been reported if cooling commences rapidly after ROSC and if performed by emergency medical personnel [Nolan *et al.* 2005; Bernard *et al.* 2002]. Hyperthermia should be averted as it is a major cause of severe neurological impairment in CA survivors [Cushman *et al.* 2007]. Based on the initial studies a number of contraindications to MTH are listed in the current literature. These include systemic infection, cardiogenic shock, coagulation disorders (previous thrombolysis not included), established multiple organ failure and pregnancy [Nolan *et al.* 2008] (Table 6).

Implementation of guidelines

Although, several registries have been founded to follow up the use of MTH after CA and patient outcome, the implementation of guidelines in every day practice is still poor [Zeiner *et al.* 2001]. Despite recent developments, it remains unclear to what extent physicians have begun to use this treatment modality. In a recent practice survey addressing the use of hypothermia after CA in the USA, 87% of the responders practicing emergency medicine, critical care, or cardiology had not used it [Abella *et al.* 2005]. In a similar survey a year later, the percentage of nonusers was 74% in the USA, 69% in Great Britain, and 39% in Finland [Merchant *et al.* 2006]. A recent survey of Canadian emergency physicians confirmed the above discouraging results reporting that only 50% of them used therapeutic hypothermia in every day practice [Kennedy *et al.* 2008]. The list of reasons of why physicians have not used hypothermia include lack of awareness of supporting data, technical constraints, and the lack of incorporation of a hypothermia protocol into advanced life support (ALS) as well as the decreased visibility of therapeutic hypothermia recommendations amongst the abundant guideline documents [Brooks and Morrison, 2008].

Conclusion: gaps in evidence

MTH represents a proven life-saving therapy which can be safely applied to post-CA syndrome patients. Comatose adult patients with ROSC

after out-of-hospital VF CA should be cooled to 32–34°C for at least 12–24 hours. Clinical data suggests that it might be beneficial for comatose survivors of in-hospital CA or cardiac arrhythmias other than VF or ventricular tachycardia [Oddo *et al*. 2008; Sandroni *et al*. 2007]. However, large randomized studies addressing therapeutic hypothermia in patients with such characteristics have not thus far appeared. The decision to withhold MTH has to balance risks and benefits in every individual patient. As an example, there is now good evidence that MTH is applicable in patients with cardiogenic shock [Skulec *et al*. 2008]. Hovdenes and colleagues also documented the safety of mild hypothermia in patients in shock after successful resuscitation from VF [Hovdenes *et al*. 2007]. Recently several publications appeared which emphasize the successful application of MTH in patients with ST elevation myocardial infarction, CA and a primary percutaneous coronary intervention (PCI) [Kurisu *et al*. 2009; Wolfrum *et al*. 2008]. This proved to be safe and practical as it was attained without delaying door-to-balloon time [Wolfrum *et al*. 2008]. Despite the lack of publications, the use of MTH can be encouraged after ROSC in cardiac surgical settings, as cardiac surgical teams are already familiar with various aspects of hypothermia and rewarming [Chakravarthy, 2009].

Considerable clinical evidence has demonstrated the safety and feasibility of cooling of patients after large strokes [Jian *et al*. 2003]. Hypothermia reduces the volume of infarct and may preserve and restore the at-risk neurons in the penumbra in focal ischemic brain injury. Rewarming appears to be associated with severe intracranial pressure elevation and brain edema affecting survival [Marion and Bullock, 2009]. The efficacy of therapeutic hypothermia for ischemic stroke has not yet been established by definitive prospective randomized clinical trials [Den Hertog *et al*. 2007; Konstas *et al*. 2006] and the 2007 American Stroke Associations Guidelines consider therapeutic hypothermia for ischemic stroke to be level IIIb evidence.

In patients with traumatic brain injury, there is strong evidence to support the use of MTH in order to maintain a reduced threshold of intracranial pressure [Marion and Bullock, 2009]. However, there were several studies where the control of ICP was not related with improved functional outcome, something that was attributed to rapid posthypothermic rewarming [Alzaga *et al*. 2006; Bernard and Buist, 2003]. The results of these studies emphasize that, if hypothermia is used to manage intracranial hypertension, rewarming must be accomplished slowly and, ideally, over the course of 12–24 h or more, otherwise sudden vasodilation leads to rebound increases in intracranial pressure [Gal *et al*. 2002; Clifton *et al*. 2001].

Unresolved issues concerning the use of therapeutic hypothermia in CA remain regarding patient selection (children, neonates), optimal timing, duration and depth of cooling, CA extent at the time of intervention and methods to minimize hypothermia-related complications or which is the best way to rewarm patients. The most favorable depth and duration of hypothermia and the consequence of the rewarming rate on neurological recovery are unknown [Janata and Holzer, 2009]. The optimal strategy is probably to keep it simple and safe without forgetting that only systematic treatment protocols improve outcomes in post-CA syndrome.

The encouraging results of different registries and prospective studies, a few months after the ILCOR/AHA statement was released regarding the utilization of MTH in post-CA syndrome, show that MTH in every day practice overrides the obstacles, offering better results in the treatment of critical patients. Sayre and colleagues have recently shown that the application of MTH according to the 2005 AHA guidelines improves the neurological outcomes after CA [Sayre *et al*. 2009].

A recent well-designed review study with MTH patients found that they were more likely to leave hospital without major brain damage and they were more likely to survive to hospital discharge [Arrich *et al*. 2009]. No cooling-specific adverse events were reported. In several countries, many efforts have been made to improve resuscitation treatments and incorporate MTH successfully in resuscitation protocols [Castrejón *et al*. 2009; Takeuchi *et al*. 2009]. Innovative cooling techniques such as intracardiopulmonary resuscitation hypothermia with and without volume loading are currently under experimental investigation and have already shown promising results [Yannopoulos *et al*. 2009]. Better understanding of the pathophysiology of resuscitation and the injury processes on which hypothermia acts and supporting critical and emergency care provider's participation to encourage guideline

implementation will serve to further promote the use of this hopeful method to save lives.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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