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# Therapeutic Hypothermia in Cardiac Arrest Survivors

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## 1. Introduction

In Europe, cardiac arrest is the leading cause of death. Summary data indicate that the annual incidence of out-of-hospital cardiac arrest (OHCA) treated by Emergency medical systems is 38 per 100,000 population (Atwood et al., 2005). Survival is an estimated 10 % for all initial rhythms. Return of spontaneous circulation (ROSC) is followed by the development of post-cardiac arrest syndrome (PCAS), including post-cardiac arrest brain injury. This has been identified as the main cause of death and the condition limiting a long term quality of life (Edgren et al., 1994). Therapeutic hypothermia (TH) has become a cornerstone of early post-resuscitation care in cardiac arrest survivors (Nolan et al., 2008). So far, it has been the only known post-cardiac arrest intervention which can reduce the risk of unfavourable neurological outcome and decrease mortality. After an advisory statement of the International Liaison Committee on Resuscitation endorsed the use of TH in 2003, it was recommended as a standard therapeutic procedure in cardiac arrest patients in the 2005 and 2010 guidelines for resuscitation and emergency cardiac care of the European Resuscitation Council and the American Heart Association (Nolan et al., 2005; Deakin et al., 2011). Accurate and safe management during the procedure of TH is a prerequisite for achieving the optimal neuroprotective effect. Moreover, the combination of TH along with other procedures (urgent myocardial revascularization, goal-directed haemodynamic support, control of blood glucose, ventilation and seizures) improves the goal of reaching a good neurological outcome (Sunde et al., 2007). This chapter summarizes pathophysiological aspects of PCAS, the evidence supporting TH and significant aspects of its practice.

## 2. Pathophysiology of post-cardiac arrest syndrome

The return of spontaneous circulation after severe complete whole-body ischemia is an unnatural pathophysiological state created by successful cardiopulmonary resuscitation. It is followed by a number of undesirable processes leading to the development of PCAS. The following four key clinical components of PCAS have been identified: a) post-cardiac arrest brain injury, b) post-cardiac arrest myocardial dysfunction, c) systemic ischemia/reperfusion response, and d) persistent precipitating pathology (Nolan et al., 2008). While some of the processes develop very early during cardiac arrest, others follow

later on after the return of spontaneous circulation, thus allowing potential space for therapeutic intervention.

Post-cardiac arrest brain injury is the most serious condition limiting long term quality of life of cardiac arrest survivors. Figure 1 summarizes the mechanisms leading to this condition (Škulec R et al., 2009).

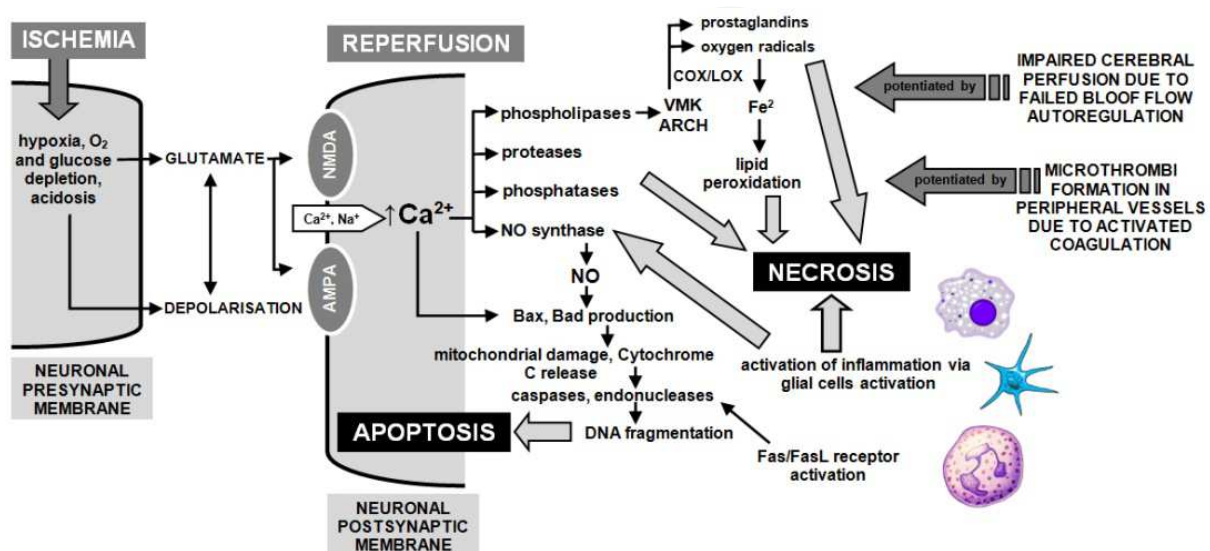


Fig. 1. Cellular and subcellular mechanisms of post-cardiac arrest brain injury.

ATP ... adenosine triphosphate, NMDA ... N-methyl-D-aspartate receptor, AMPA ... amino-3-hydroxy-5-methylisoxazole-4-propionate receptor, NO ... nitric oxide, VMK ... free fatty acids, ARCH ... arachidonate, COX ... cyclo-oxygenase, LOX ... lipo-oxygenase, DNA ... deoxyribonucleic acid.

Triggering of the glutamate neuroexcitatory cascade plays a crucial role. Cardiac arrest leads to excessive glutamate release followed by an overflow of calcium to neurons via N-methyl-D-aspartate receptor stimulation. This is a potent trigger of the metabolic and inflammatory pathways causing neuronal necrosis and apoptosis. Increased intracellular calcium pool activates phosphatases and proteases, which causes neuronal damage, phospholipases responsible for oxygen free radical formation and nitric oxide synthase activation, which enhances proinflammatory nitric oxide production. Nitric oxide also opens the apoptotic pathway via activation of proapoptotic genes of the Bcl-2 family, causing mitochondrial damage, cytochrome C release, activation of caspases and endonucleases resulting in DNA fragmentation and programmed neuronal death. Glial cell activation potentiates an undesirable proinflammatory cascade. This very complex deleterious response to global cerebral ischemia is amplified by impaired cerebral perfusion due to failed blood flow autoregulation and by microthrombi formation in small vessels due to activated coagulation (Nolan et al., 2008).

Post-cardiac arrest systolic and diastolic myocardial dysfunction is a common phenomenon of multifactorial origin. It is supposed that decreased cardiac output may contribute to the unfavourable outcome (Laver et al., 2004). Myocardial stunning has been identified as the main underlying mechanism (Laurent et al., 2002; Checchia et al., 2003). Moreover, myocardial dysfunction may be worsened through the administration of high doses of

adrenaline during CPR (Tang et al., 1995). On the other hand, post-cardiac arrest myocardial stunnig is a reversible condition and can be reversed by catecholamines (Vasquez et al., 2004).

Critical whole-body ischemia during cardiac arrest, even if followed by successful reperfusion, is a very potent trigger for the whole-body immune system response. It is termed the systemic inflammatory response syndrome (SIRS) and represents a serious condition related to systemic inflammation and organ dysfunction. The underlying mechanism for development of SIRS is induced cytokine storm accompanied by activation of leucocytes and platelets, endothelial dysfunction and coagulopathy. Relative acute adrenal insufficiency may worsen the course of the disease (Hékimian et al., 2004).

Cardiac arrest does not develop on it’s own but it is a complication of other underlying diseases. Persistent precipitating pathology may have a negative impact on further outcome, especially when it is a critical disease like extensive acute myocardial infarction, massive pulmonary embolism, etc.

3. Underlying mechanisms of protection by therapeutic hypothermia

Hundreds of substances have been studied to find some with clinically signifiant neuroprotective effect. However, promising pilot experimental results were always followed by further experimental or clinical failure. It is generally considered that the main reason for failure is the complexity of ischemia-reperfusion injury which can not be attenuated or reversed by a substance affecting only one specific metabolic pathway. On the other side, hypothermia is a robust non-specific intervention having an impact on all processes of ischemia reperfusion injury simultaneously.

<ul style="list-style-type: none"><li>• antiedematic effect<ul style="list-style-type: none"><li>adjustment of cerebral blood flow to metabolic demand</li><li>reduction of vascular permeability</li><li>blood-brain barrier stabilizing effect</li></ul></li><li>• cellular protection<ul style="list-style-type: none"><li>dna preservation from oxygen free radical-mediated damage</li><li>cell membrane stabilizing effect</li><li>prevention of mitochondrial dysfunction</li></ul></li><li>• antiapoptotic effect<ul style="list-style-type: none"><li>inhibition of caspase activation</li><li>prevention of cytochrome c release</li></ul></li></ul>	<ul style="list-style-type: none"><li>• anti-inflammatory effect<ul style="list-style-type: none"><li>supression of oxygen free radical formation</li><li>decrease of intracelullar calcium</li><li>supression of nitric oxide production</li><li>supression of interleukin 6 production</li><li>reduces production of matrix metalloproteinases</li><li>supress neutrophil and microglia activation</li></ul></li><li>• supression of cerebral metabolism<ul style="list-style-type: none"><li>inhibition of glutamate excessive release</li><li>decrease of oxygen and glucose consumption</li><li>attenuation of thermo-pooling phenomenon</li></ul></li></ul>
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Table 1. Proposed neuroprotective mechanisms of therapeutic hypothermia.

Hypothermia reduces cerebral metabolism by 7 % for each degree Celsius reduction in Body Temperature (BT) and reduces whole-body energy demand (Erecinska et al., 2003). Other mechanisms which play a role in hypothermia-induced neuroprotection are listed in table 1 (Ostadal, 2009; Polderman, 2009; Liu & Yenari, 2007; Busto et al., 2007; Kataoka & Yanase, 1998; Globus et al., 1995; Lei et al., 1994; Xu et al., 2002; Huang et al., 1999; Fischer et al., 1999).

4. Clinical studies

Even though the idea of neuroprotection by decreasing body core temperature is not new, its implementation became sustainable in 2002, when the results of two crucial randomized clinical trials were published. Both were of similar design and reached analogical results, strongly supporting post-cardiac arrest cooling (table 2).

The European Hypothermia After Cardiac Arrest (HACA) multicenter trial has been the largest one (Hypothermia after Cardiac Arrest Study Group, 2002). A total of 275 patients who had been resuscitated from cardiac arrest due to ventricular fibrillation or pulseless ventricular tachycardia was randomised to conventional therapy or to induced mild hypothermia of 32 – 34 °C for 24 hours. In addition to a significant neuroprotective clinical effect, mortality at 6 months was 41 % in the hypothermia group, as compared with 55 % in the normothermia group (RR 0.74; CI 95% 0.58-0.95, p<0.05).

In the Australian study by Bernard et al, 77 patients succesfully resuscitated from cardiac arrest of presumed cardiac arrest origin, having ventricular fibrillation or pulseless ventricular tachycardia as an initial rhythm,were assigned to mild hypothermia of 32 – 34 °C for 12 hours or to standard treatment (Bernard et al., 2002). In the hypothermia group, more patients reached the favourable neurological outcome (cerebral performance category score 1 or 2) at hospital discharge than in the control group. In both studies, there was no significant diference in the frequency of adverse events.

	HYPOTHERMIA GROUP (%)	STANDARD TREATMENT GROUP (%)	RELATIVE RISK	P
favourable neurological outcome at hospital discharge				
HACA Study Group Trial	53	36	1.50	0.006
Bernard et al.	49	26	1.75	0.052
favourable neurological outcome at 6 months				
HACA Study Group Trial	52	36	1.44	0.009

Table 2. Outcomes of therapeutic hypothermia in randomized clinical studies.

Following this, a series of clinical studies have confirmed a positive role of TH in post-cardiac arrest care. It was also shown that a close relation of TH with other interventions such as control of blood glucose, haemodynamics, ventilation and handling of seizures can improve long term survival of patients (Sunde et al., 2007; Knafelj et al., 2007; Nolan et al, 2009).



Analyses of the registries confirmed the results of clinical studies (Oksanen et al., 2007; Arrich, 2007). Several meta-analyses have however produced inconsistent results (table 3). While Holzer et al calculated that six patients have to be treated by TH to save one more life (95% CI 4-13,  $p < 0,05$ ), Nielsens meta-analysis pointed out to some gaps in the evidence (Nielsen et al., 2010). Anyway, we have still quite firm evidence compared to other commonly used procedures in intensive care medicine.

AUTHOR	TYPE OF THE ANALYSIS	NUMBER OF THE PATIENTS	DISCHARGE NEUROLOGICAL OUTCOME	6 MONTHS NEUROLOGICAL OUTCOME	HOSPITAL MORTALITY
Arrich, 2008	registry	650	TH: 45%* NO TH: 32%	-	TH: 57%* NO TH: 32%
Oksanen et al., 2007	registry	1555	-	-	TH: 44,6%
Holzer et al., 2006	metaanalysis	385	RR 1.68, 95%CI 1.29-2.07 favouring TH*	RR 1.44, 95% CI 1.11-1.76 favouring TH*	-
Nielsen et al., 2010	metaanalysis	478	RR 0.78, 95% CI 0.64-0.95 favouring TH*		RR 0.84, 95%CI 0.70-1.01 favouring TH

TH...therapeutic hypothermia, RR...relative risk, CI...confidence interval, \*... $p<0.05$

Table 3. The results of the analyses of the registries and metaanalyses.

5. Indications and contraindications

Therapeutic hypothermia is indicated in successfully resuscitated cardiac arrest patients, persistence of coma and requirement of mechanical ventilation. While there is good evidence supporting cooling of out-of-hospital adult cardiac arrest patients presenting with ventricular fibrillation, induction in other groups of in-hospital cardiac arrest patients, such as those with non-defibrillating initial rhythm and pediatric patients is supported by lower degrees of evidence (Holzer et al., 2006; Storm et al., 2008; Don et al., 2009; Polderman et al., 2003; Biarent et al., 2010; Testori et al., 2011). Nevertheless, clinical, experimental and patophysiological data suggest that hypothermia may also have protective effects in patients other than those with ventricular fibrillation OHCA. Therefore, it may be considered reasonable to also use TH in these groups.

Experimental data suggest that TH should be started as soon as possible after ROSC. Thus, in OHCA patients, pre-hospital initiation of cooling appears to be a method of choice and this is discussed further. On the contrary, there is weak evidence of what is an acceptable delay from ROSC to start chilling. It is generally considered that it should not be delayed more than 6 hours.

There is not any general agreement on contraindications to TH and there are differences among the guidelines. However, Table 4 lists all conditions we should keep in mind.

CONTRAINDICATIONS TO THERAPEUTIC HYPOTHERMIA
<ul style="list-style-type: none"><li>• established multiple organ failure or underlying terminal illness</li><li>• pre-existing coagulopathy</li><li>• severe systemic infection</li><li>• severe active bleeding</li><li>• patient conscious after short cardiopulmonary resuscitation</li><li>• do-not-resuscitate or do-not-intubate status</li><li>• coma of origin other than cardiac arrest</li><li>• circulatory failure defined as hypotension irresponsive to volume expansion and/or vasopressoric support and/or mechanical circulatory support</li><li>• cardiac arrest of traumatic origin</li><li>• preexisting hypothermia &lt;34 °C</li><li>• pregnancy</li></ul>

Table 4. Contraindications of therapeutic hypothermia.

The use of TH in children has been classified as a class IIb recommendation by pediatric guidelines 2005 and the recent guidelines have accepted this treatment in children too (Polderman et al., 2001; Losert et al., 2008). Therefore, pediatric cardiac arrest patients should not be excluded from the candidates for PTH.

**6. Therapeutic hypothermia in the setting of acute myocardial infarction and PCI**

Acute myocardial infarction (AMI) is the most common cause of cardiac arrest.. In a patient with cardiac arrest caused by AMI, there may arise several questions:

- What is more important and what should be preferred – TH or percutaneous coronary intervention (PCI)?
- Does TH induction interfere with the angiographic result of PCI?
- Should the patient planned for TH be treated by antithrombotics and / or thrombolytics?
- What is the impact of TH on myocardial function altered by AMI and cardiac arrest?

First, it should be noticed that successfully resuscitated cardiac arrest patient with AMI must be considered as a critically ill patient in general and not onlyanAMI patient. Therefore, PCI must not cause a delay of initiation of cooling and it is even more paramount vice versa. Performance of both procedures in parallel has been shown to be feasible and safe and PCI centers should establish TH in the catheterization laboratory as routine procedure (Koester et al., 2011). The use of common cooling methods do not interfere with the procedure of cardiac catheterisation.

Second, there is evidence, that the concomitant use of TH does not compromise angiographic results of PCI (Noc, 2010). Moreover, several studies have demonstrated, that

PCI performed during TH is not associated with an increased rate of major bleeding events (Schefold et al., 2009; Knafelj et al., 2007). It is an important issue because major bleeding has been shown to be a strong predictor of mortality in patients after PCI (Manoukian et al., 2007).

Third, it has been shown that antithrombotic and / or fibrinolytic therapy may be administered as the part of complex post-cardiac arrest care including therapeutic hypothermia. It is not a contraindication to TH and it should be used in accordance with the recent guidelines regardless of cooling (Van de Werf et al., 2008; Torbicki et al., 2008). On the other hand, most enzymatic processes in the body exhibit temperature dependency. Pilot studies presented alterations in the pharmacokinetics of many drugs used in critical care during TH. Antithrombotics are not an exclusion (table 5). Further studies are necessary to tailor its dosage regimen for the specific conditions during TH.

AUTHOR	DRUG	EFFECT OF HYPOTHERMIA ON METABOLISM
Michelson et al., 1999	aspirin	aspirin did not significantly augment hypothermia-induced platelet dysfunction in vivo
Bjelland et al., 2010	clopidogrel	in patients with hypothermia, absence of effect on day 1 after administration, with some improvement on day 3
Frelinger AL et al., 2003	glycoprotein IIb/IIIa antagonist	mild hypothermia augments eptifibatide- and tirofiban- but not abciximab-induced inhibition of platelet aggregation

Table 5. Effects of hypothermia on pharmacokinetics and pharmacodynamics of antithrombotics.

Fourth, it has been previously described that post-cardiac arrest myocardial dysfunction is a common phenomenon. In AMI patients, apart from myocardial stunning, myocardial ischemia due to coronary artery occlusion can play a role. There are several experimental and clinical data that TH does not ameliorate post-cardiac arrest myocardial dysfunction (Murphy et al, 2010; Hsu et al., 2009). Nevertheless, there is a room for further investigation. Complex hemodynamic clinical presentation of patients post-cardiac arrest can be the shock syndrome. It is a condition reflecting not only myocardial dysfunction but also systemic ischemia-reperfusion injury. A few studies have reported on the feasibility of TH in the setting of cardiogenic shock (Hovdenes et al., 2007; Skulec et al., 2008). Further investigation is needed but TH should be always considered in circulatory unstable patients who are responsive to volume expansion and/or vasopressoric support and/or mechanical circulatory support.

7. Protocol for practicing therapeutic mild hypothermia

Accurate and safe practicing of TH following a written protocol is a prerequisite for achieving optimal neuroprotective effect. Till now, only few papers summarizing practical procedural issues of the TH procedure in detail have been published (Bianchin et al., 2009; Škulec et al., 2010). Local therapeutic protocols differ from one to the other.



There are four phases of the therapeutic hypothermia protocol: cooling phase, maintenance phase, rewarming phase and period of control of normothermia (Figure 2).

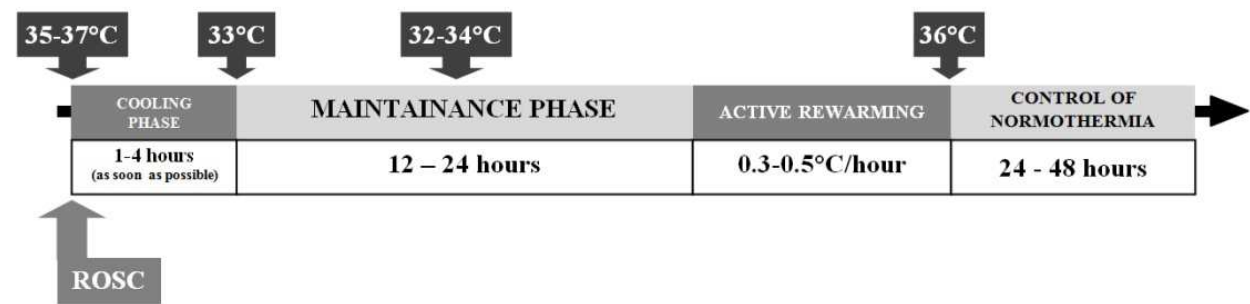


Fig. 2. The protocol for practicing therapeutic hypothermia.  
ROSC...return of spontaneous circulation.

During the cooling phase, the aim is to reach the target therapeutic temperature of 33 °C as soon as possible after the return of spontaneous circulation. This is followed by BT regulation in the therapeutic range of 32 – 34 °C for 12 – 24 hours. In randomized clinical studies, both TH durations were associated with an improved outcome. It is not known, whether one protocol is better than the other or if cooling for a longer time is better. However, durations shorter than 12 hours should be avoided. It is advisable to beware of overcooling below 32 °C for its potential association with worse outcome (Merchant et al, 2006; Škulec et al., 2008). The rewarming phase is as important as the maintenance of TH. The rewarming should not be a passive but rather an active process resulting in slow and controlled reaching of normothermia with a rewarming rate of 0.1–0.33°C/hour (Seder & Van der Kloot, 2009). It can be performed by the same technique that was used for chilling. Once a BT of 36 °C is reached, normothermia should be controlled carefully for up to 48 hours since further hypothermia may worsen the outcome.

In the course of cooling, adequate sedation should be tailored for suppression of involuntary shivering. In some patients, neuromuscular blockade can be required during the cooling and maintenance phases (Hékimian et al., 2004). In the next phases, muscle paralysis should be strictly individual to avoid adverse effects of lengthy neuromuscular blockade. After rewarming, sedatives, analgesics, and muscle relaxants should be discontinued and standard intensive care should be provided. Other drugs decreasing the shivering threshold are buspirone and meperidine.

Induction of hypothermia can evoke metabolic disturbances, especially hypokalemia, hypomagnesemia, hypophosphatemia, hypocalcemia and hyperglycemia (Michelson et al., 1994; Polderman et al., 2001; Losert et al., 2008). Therefore, regular measurements are advisable. While potassium and magnesium supplementation is favourable during the maintenance phase, calcium may worsen ischemia-reperfusion injury and permissive hypocalcemia may be tolerated. However, mild hypokalemia may be tolerated to avoid excessive increase of Potassium during rewarming. Control of Glucose levels should follow conventional rather than strict targets.

Decrease of body temperature is physiologically associated with haemodynamic changes. Relative and absolute hypovolemia, bradycardia, decrease of arterial blood pressure and cardiac output are common. In general, it is impossible to distinguish these changes from

those induced by cardiac arrest and the precipitating pathology. Anyhow, early goal directed therapy approach should be applied (Table 6), using standard procedures of volume expansion, vasopressor and/or inotropic support and/or mechanical circulatory support (Cvachovec et al., 2009).

mean arterial pressure (mm Hg)	65 – 100
systolic blood pressure (mm Hg)	> 100
central venous pressure (mm Hg)	8 – 12
diuresis (ml/kg/hour)	1
central venous oxygen saturation (%)	> 70

Table 6. Goals for early directed therapy in cardiac arrest survivors.

Peptic ulcer and deep vein thrombosis prophylaxis, oral care, positioning, ventilator setting assessment govern the same indications as in critically ill patients in general. There have been no publications recommending the timing and selection of suitable formulation of clinical nutrition in cardiac arrest patients. In most cases, it is initiated immediately after completion of the TH process (Škulec et al., 2010).

Monitoring the body core temperature (BT) should be continuous with a probe inserted in the pulmonary artery, rectum, urinary bladder or oesophagus. Pulmonary artery catheter is considered to be the gold standard for BT measurement but this should not be the only indication of pulmonary artery catheter insertion. In the absence of other conditions such as the need for invasive haemodynamic monitoring, an alternative approach should be used. Tympanic temperature is an acceptable for pre-hospital monitoring.

Key principles for proper practicing of TH are to keep patients deeply sedated to suppress shivering and watch for potential side effects of TH carefully.

8. Cooling methods

Currently, there is a wide range of cooling techniques available. They can be classified into two major groups – the methods inducing whole body hypothermia and the methods primarily targeted to local brain cooling (Table 7) (Škulec et al., 2009). The latter should be considered as a supplementary approach because evidence for outcome benefit has been registered only for whole body cooling.

In spite of the unproven superiority of device-based cooling techniques (endovascular catheter cooling, surface cooling via mattress or cooling pads), it is convenient for several reasons when compared with conventional approaches (surface cooling via ice-packs, cold intravenous infusion, cold gastric or urinary bladder lavage). It provides more reliable maintenance of target temperature including less incidence of overcooling, it is more friendly for nursing and allows control of BT even in the phase of controlled normothermia (Hoedemaekers et al., 2007; Škulec et al., 2009). However, it must be stressed that this does not disqualify conventional methods from routine practice. Pivotal clinical studies were based on simple surface cooling and its low cost predetermines it to serve as a starting method for new TH users (Hypothermia after Cardiac Arrest Study Group, 2002; Bernard et al., 2002).

METHOD	COOLING RATE	INCIDENCE OF OVERCOOLING	CLINICAL EVIDENCE	FINANCIAL COSTS
WHOLE-BODY HYPOTHERMIA				
• surface cooling				
• ice-packs	+	+++	+++	€
• water cooling mattress	++	++	+++	€€
• air cooling mattress	+	+++	+	€€
• special cooling pads	++	++	+	€€
• cold air flow	?	?	-	€
• RIVA	+++	++	+++	€
• cold gastric / urinary bladder lavage	?	?	-	€
• cold peritoneal lavage	?	?	-	?
• endovascular cathether cooling	++	+	+++	€€€
• extracorporeal circuit device	+++	?	+	€€€
LOCAL BRAIN COOLING				
• intranasal cooling	+ (++ brain)	?	+++	?
• cooling cap / helmet	+ (++ brain)	?	+	?

RIVA...rapid intravenous administration of cold crystalloids  
+...low cooling rate, incidence of overcooling or clinical evidence, +++...high cooling rate, incidence of overcooling or clinical evidence, €...low financial costs, €€€...high financial costs

Table 7. Cooling methods.

Surface cooling techniques are used most commonly. There is a variety of different modifications: simple ice-packs, more effective manufactured precooled special pads and sophisticated devices with automated feedback control of BT, chilling via gel pads or a cooling mattress (figures 3 and 4).

The method of rapid intravenous administration of cold crystalloids (RIVA) has been found efficient, simple and safe. Infusion of 15 – 30 ml/kg of 4 °C cold crystalloid (normal saline, Ringer solution, Hartmann solution) at an infusion rate >60 ml/h may induce the decrease of BT >1.4 °C (Kim et al., 2005; Kim et al., 2007; Kliegel et al., 2005; Kliegel et al., 2007; Virkkunen et al., 2004; Kämäräinen et al., 2008; Bernard & Rosalion, 2008; Bruel et al., 2008; Polderman et al., 2005; Vanden Hoek et al., 2004). However, additional cooling techniques are necessary for TH maintainance (Kliegel et al., 2007).

Endovascular catheter cooling is a highly sophisticated method of invasive cooling with a cooling rate 1.0 – 1.5 °C/h (Škulec et al., 2009). It is performed by inserting the cooling catheter into the inferior vena cava using the femoral approach. Circulation of cold normal saline through the catheter is directed by an extracorporeal unit to reach a satisfactory cooling rate and an excellent temperature stability of the patient (figure 5) (Hoedemaekers et al., 2007).

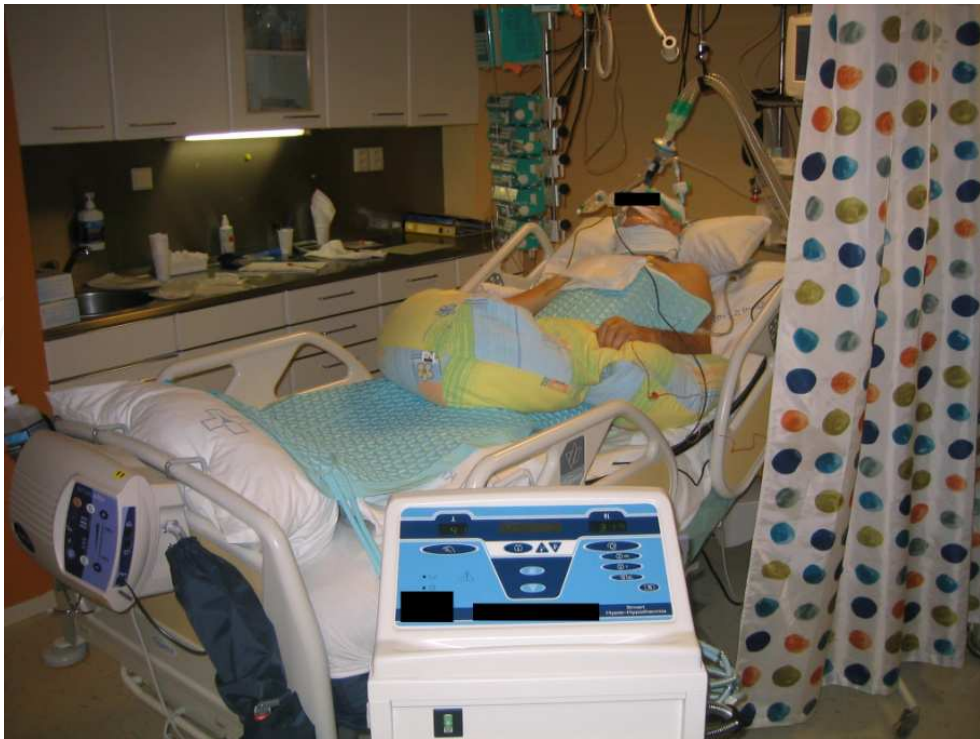


Fig. 3. Water cooling mattress system Blanketrol III, Cincinnati Sub-Zero Products, Inc., Cincinnati, USA. Published with the permission of P. Telekes, M.D., Cardiac Center, Liberec Hospital, Czech republic.



Fig. 4. Highly effective cooling pads EMCOOLS pad, EMCOOLS, Emergency Medical Cooling Systems AG, Vienna, Austria, with the permission.





Fig. 5. Endovascular catheter cooling via CoolGard 3000TM and Icy femoral cathether TM, Alsius Corp., Irvine, USA. Published with the permission of P. Ostadal, M.D., PhD., Department of Cardiology, Na Homolce Hospital, Czech republic.

It can be used also for controlling normothermia after the rewarming phase and guide the patients through the whole early post-resuscitation period. Cooling efficacy and safety was documented not only for cardiac arrest patients but also for patients with traumatic brain injury, stroke and acute myocardial infarction (Diringer et al., 2004; Schmutzhard et al., 2002; Lyden et al., 2005; Guluma et al., 2008; Georgiadis et al., 2001; Keller et al., 2003; De Georgia et al., 2004; Dixon et al., 2002; Kandzari et al., 2004; Stone et al., 2006). Dixon et al. randomized 42 patients with AMI to primary PCI with or without endovascular cooling (target core temperature 33 degrees C) for 3 hours after reperfusion. Reduction of infarct size was not identified but the study confirmed the safety of endovascular cooling as an adjunct to primary PCI. Kandzari et al. reached similar results in a nonrandomized study of 18 patients.

Intranasal cooling is a new and safe method to easily cool down the brain. It is a very simple method with minimal burdening of the staff (Castrén et al., 2010). Like RIVA, it is convenient for the rapid induction of TH and suitable for pre-hospital care and emergency medicine departments.

There are many other experimental thermoregulatory methods. Some of them, like cardiopulmonary bypass, femorocarotic bypass with extracorporeal cooling of blood, peritoneal cooling or total liquid ventilation cooling are too invasive and/or complicated in comparison with the current effective techniques (Reed et al., 2002; Mori et al., 2001; Hong et al., 2002; Xiao et al., 1995). The others are just in the beginning of their development and perhaps represent the future. On the gate of science-fiction stands the possibility of pharmacological induction of hibernation. Hibernation is a behavioural, physiological, and molecular adaptation exhibited by diverse mammalian species to withstand protracted periods or seasons of insufficient or unpredictable food availability (Kelly, 2007). Distribution of this process amongst different species argues that hibernation genes required for hibernation are common to all mammals (Srere et al., 1992). Such capacity to profoundly

decrease the metabolic demand of organs and tissues has the potential to translate into a novel approach to prevention of ischemia-reperfusion injury. Neurotensin and its analogies are studied as potential triggers of this process (Schneider et al., 2006).

9. Side effects of cooling

TH treatment may be associated with adverse events (Table 8) (Polderman et al., 2009; Skulec et al., 2008; Nielsen et al., 2009). These are related to the cooling device or caused by hypothermia itself. While the former are rare, the latter are quite common. However, we should keep in mind the fact that some of them are physiological responses to hypothermia rather than avderse events.

	FREQUENCY (%)
pneumonia	40 – 50
any arrhythmias	33
recurrence of cardiac arrest	7 – 11
metabolic disturbances	
sustained hyperglycaemia >8 mmol/l	37
hypokalaemia <3 mmol/l	18
hypomagnesaemia	18
hypophosphataemia	19
hyperamylasaemia	12
seizures	24
major bleeding	3 – 6
sepsis	4

Table 8. Adverse effects of therapeutic hypothermia (Nielsen et al., 2009).

Often, it is not possible to distinguish whether the event is caused by hypothermia or by post-cardiac arrest syndrome itself. This is especially the case of post-cardiac arrest shock syndrome. It may affect as much as 18 – 50% of cardiac arrest patients. Although TH induces cold diuresis, hypovolemia, bradycardia and decrease of cardiac output, post-cardiac arrest myocardial dysfunction and precipitating pathology arises independently of TH and all must be treated together. It was shown that TH does not worsen the course of the disease even in the presence of shock syndrome (Škulec et al., 2008). Pneumonia, cardiac arrhythmias, metabolite disturbances and seizures have been identified as the most common adverse events of cooling.

Recently, Nielsen et al analyzed a set of 765 patients and identified that sustained hyperglycaemia and seizures are associated with increased mortality while other adverse events are not (Nielsen et al., 2011). Randomized clinical studies showed comparable incidence of adverse events except for pneumonia and sepsis, which exhibited a trend of increased appearance in cooled patients (Hypothermia after Cardiac Arrest Study Group, 2002; Bernard et al., 2002).



Device related adverse events depend on the cooling method. Surface cooling may be complicated by frostbite, the RIVA method may lead to volume overload and pulmonary oedema, endovascular catheter cooling may be complicated by deep venous thrombosis (Škulec et al., 2009). The occurrence of these can be minimized by proper and careful practicing of TH.

## 10. Complex post-cardiac arrest intensive care

An intensivist should be aware of the fact that TH is not a self-salvable technique after cardiac arrest. Care must be contextualized to the complex neuroprotective and cardioprotective post-cardiac arrest support. The main components are:

- therapeutic hypothermia,
- urgent coronary angiography and PCI if indicated,
- control of blood glucose,
- early haemodynamic goal-directed therapy,
- control of normoventilation,
- control of seizures.

It has been shown by Sunde et al that a transition from the conventional passive approach to the standardised active treatment protocol including all mentioned items can improve prognosis of the patients (Sunde et al., 2007). Further studies have confirmed this observation (Škulec et al., 2008; Tømte et al., 2011; Werling et al., 2007). Thus, it is of major importance to consider every cardiac arrest patient as to be like any other critically ill patient requiring complex, active and protocolized therapy, beyond the scope of isolated TH procedure.

The most sophisticated component of such approach is the ensurance of availability of immediate coronary angiography and PCI. At present, the discussion is held whether all OHCA patients should be transferred to cardiac arrest centers with PCI facility or not. To answer this question needs further studies. Nevertheless, all patients with supposed cardiac origin of cardiac arrest are candidates of such approach and those with ST elevation acute myocardial infarction undoubtedly.

There is an association between post-cardiac arrest hyperglycaemia and poor neurological outcome. However, tight glucose control (4.5 – 6.0 mmol/l) should not be practiced after cardiac arrest because of the increased risk of hypoglycaemia. Blood glucose should be maintained at  $\leq 10$  mmol/l (Padkin, 2009; Deakin et al., 2010).

Early haemodynamic goal-directed therapy has been shown to improve prognosis of patients with severe sepsis and septic shock (Rivers et al., 2001). There is limited evidence that this approach can be also beneficial to cardiac arrest survivors (Gaieski et al., 2009). Reasonable goals are listed in table 4.

Several reasons make control of normoventilation an important part of post-cardiac arrest care. Firstly, while during cardiopulmonary resuscitation we should maintain FIO<sub>2</sub> of 1.0, it is not the setting for post-cardiac arrest care. There is a body of preclinical evidence that hyperoxia may worsen neuronal ischemia-reperfusion injury by augmenting oxidative stress (Balan et al., 2006). On this basis, it is recommended to eliminate hypoxia but

unnecessary hyperoxia should be avoided. This can be achieved by adjusting the  $\text{FiO}_2$  to produce an arterial oxygen saturation of 94 – 96% (Nolan et al., 2008). Secondly, in brain-injured patients, cerebral vasoconstriction caused by hyperventilation may induce cerebral ischaemia (Coles et al., 2007). Hyperventilation also decrease cardiac output via increased intrathoracic pressure (Aufderheide & Lurie, 2004). On the other hand, hypoventilation may cause hypoxia and hypercapnia could increase intracranial pressure and cause acidosis. Therefore, ventilation should be adjusted to achieve normocapnia and should be monitored by regular measurement of arterial blood gas values (Nolan et al., 2008).

Seizures and/or myoclonus occur in 10–40% of successfully resuscitated comatose cardiac arrest patients. It increases oxygen demand dramatically and may aggravate neurological injury (Ingvar, 1986). It should be treated after the first event and followed by maintenance therapy. Drugs of choice are benzodiazepines, phenytoin, sodium valproate, propofol, or a barbiturate (Nolan et al., 2008). Preventive treatment has not been studied yet.

Treatment of other conditions like adrenal dysfunction, organ dysfunctions and infection therapy do not differ from common practice in critically ill patients.

## 11. Pre-hospital cooling

It has been recommended that the target therapeutic temperature should be reached as soon as possible (Safar, 2002). In successfully resuscitated out-of-hospital cardiac arrest (OHCA) patients, pre-hospital initiation of cooling appears to be the method of choice. However, initiation of cooling in the field is not a simple shift of in-hospital procedure to pre-hospital area. A pre-hospital emergency team frequently operates in demanding conditions and is engaged in the process of cardiopulmonary resuscitation, early post-cardiac arrest stabilisation and decision on transport direction. Therefore, pre-hospital cooling calls for a very simple, efficient and safe cooling method and its usage should not cause a transport delay. A background of regional hospitals practicing TH is essential to ensure cooling continuity.

A few studies demonstrating the efficacy and safety of this strategy, predominantly for the RIVA method, have been published (Kim et al., 2007; Kämäräinen et al., 2008). When performed properly, it can decrease BT by  $>1.4^\circ\text{C}$  during transport. Moreover, a dose of 10 – 20 ml/kg of cold normal saline can contribute to hemodynamic stabilization. In addition, this way of cooling exhibits an excellent safety profile with minimal risk of volume overload. Considering its simplicity and low costs, the RIVA method is the first choice for pre-hospital cooling (Figure 6).

A major barrier for a wide recommendation of pre-hospital cooling in successfully resuscitated OHCA patients is the absence of clear evidence of the outcome benefit. Apparently, improved survival is not related to pre-hospital hypothermia itself but to the close coupling of PTH with its in-hospital continuation (Škulec et al., 2010; Castrén et al., 2010). In any case, a large randomized trial is required.

Considering the pros and cons, at present, in the setting of proper collaboration of the emergency medical service and the target in-hospital facility, it is justifiable to implement prehospital cooling even in the absence of unambiguous evidence to support this practice.

Other possibilities suitable for pre-hospital cooling include surface cooling via manufactured cooling pads and intranasal local brain cooling.



Fig. 6. Refrigerator in the ambulance car with supply of cold saline.

12. Worldwide implementation of therapeutic hypothermia

Nine years have elapsed since randomized clinical studies allowing the use of TH were published. During this period, in-hospital TH utilisation has varied from 8 to 95 % in different countries until now (figure 7) (Škulec et al., 2010).

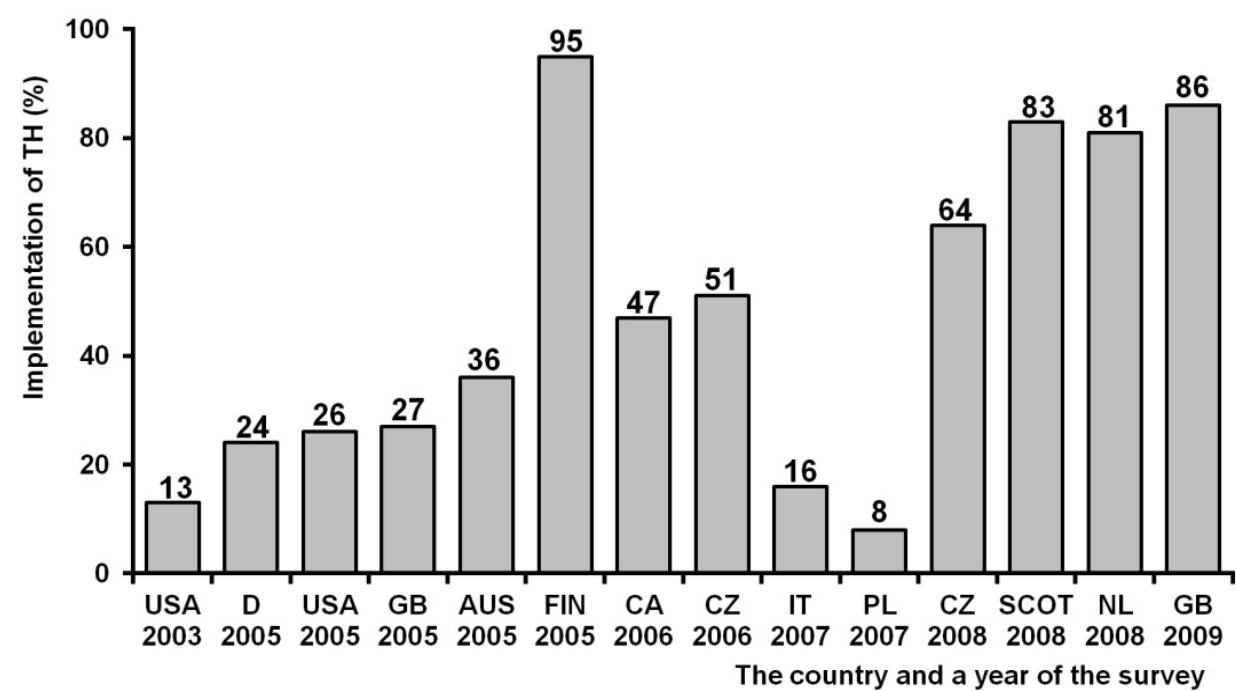


Fig. 7. TH implementation in different countries in the last years.  
USA...United States of America, D...Germany, GB...Great Britain, AUS...Australia, FIN...Finland, CA...Canada, CZ...Czech republic, PL...Poland, SCOT...Scotland, NL...Netherlands, TH...therapeutic mild hypothermia

More or less, implementation has increased over the years. Nevertheless, there are a lot of challenges and room for improvement. Firstly, effort should be focused on enhancing the frequency of TH application in every ICU. Secondly, unavailability of cooling techniques should not be a barrier for TH implementation, it is reliable to start with low-cost simple conventional cooling methods (RIVA, surface cooling). Thirdly, growth of TH implementation has to progress hand in hand with the quality of provided care. The method must be protocol-guided, respecting clear indications and contraindications and applying complex neuroprotective and cardioprotective post-cardiac arrest care.

### 13. Alternative thermoregulation strategies in cardiac arrest survivors

There are two alternative thermoregulation neuroprotective strategies other than post-cardiac arrest cooling: intra-arrest cooling and a principle of emergency preservation and resuscitation (also called suspended reanimation).

Animals experiments showed that early intra-arrest initiation of cooling resulted in significantly better neurological outcome than cooling after return of spontaneous circulation (Abella et al., 2004; Kuboyama et al., 1993). This concept was also evaluated in a few clinical studies. RIVA method was very effective but clinical outcome was inconclusive (Kämäräinen et al., 2008; Bruel et al., 2008). More promising seems to be the method of intranasal cooling. The recent PRINCE study revealed its safety, effectivity and suggested outcome improvement (Castrén et al., 2010). A large outcome trial is ongoing. Nevertheless, it must be stressed that intra-arrest cooling intervenes in standard cardiopulmonary resuscitation while cooling after return of spontaneous circulation does not. Therefore, intra-arrest cooling should be reserved only for clinical studies, until the clinical benefit is clearly proved.

Emergency preservation and resuscitation is a novel approach supposed to treat victims of exsanguination cardiac arrest. Management is to be as follows: a cold aortic flush is used to induce deep hypothermic preservation in the field followed by transport to hospital facility for emergent surgical treatment and delayed resuscitation with cardiopulmonary bypass (Drabek, 2007). This approach has been tested in animal experiments and stands at door of clinical studies.

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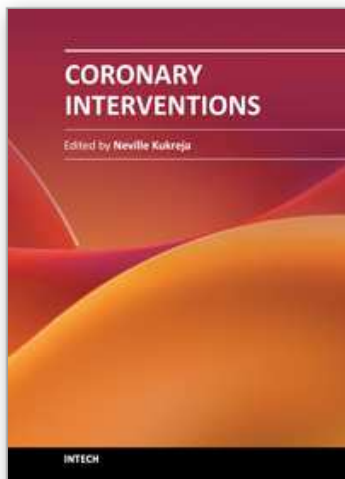
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