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Advances in Post Resuscitation Care: 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 postresuscitation care of comatose survivors of cardiac arrest. Two randomized, controlled clinical trials published in the *New England Journal of Medicine* showed that after resuscitation mild hypothermia lowers mortality, improves neurological outcome after successfully treated cardiac arrest, and is recommended by the 2005 update guidelines of International Liaison Committee on Resuscitation and European Resuscitation Council (ERC). In the present article pathophysiological mechanisms of hypothermia, cooling methods and potential side effects are briefly discussed. Questions regarding implementation of therapeutic hypothermia recommendations in every day clinical practice and future investigation are also addressed.

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INTRODUCTION

Out of hospital cardiac arrest (CA) affects more than 375000 individuals per year in Europe [1], while it carries a greater than 90% mortality rate, leading to over 300,000 deaths in the United States each year [2]. 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 [3]. 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 [4]. Therapeutic hypothermia has been used in surgical procedures for decades. The means by which hypothermia provides neuroprotection are uncertain, but preliminary studies suggested that mild induced hypothermia (MIH) could improve cardiological and neurological outcome in patients who suffered CA, while MIH side-effects could successfully be managed in modern intensive care units (ICU).

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THERAPEUTIC HYPOTHERMIA AFTER CARDIAC ARREST

A number of landmark studies and a metanalysis, published over the past few

years, have demonstrated that cooling patients can provide significant survival benefit after initial resuscitation from CA [5-8]. The European HACA trial group demonstrated an improvement in survival to hospital discharge with favorable neurological status in cooled patients compared to normothermic patients surviving arrest (53% vs. 36%, respectively), with no significant adverse events from cooling [5]. In the Australian study carried out by Bernard et al there was a significant difference in the rate of good neurological outcome: 21 of 43 patients (49%) in the hypothermia group vs. 9 of 34 patients (26%) in the normothermia group [6]. In a previous, limited size clinical trial by Hachimi-Idrissi et al 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 [7] (Table 1). Several of these MIH investigations were well-designed randomized controlled trials, providing better evidence for the use of cooling than many pharmacologic interventions after CA [8]

On the strength of these studies, the International Liaison Committee on Resuscitation (ILCOR) and the American Heart Association/European Resuscitation Council in the 2005 published guidelines [9,10] recommend that:

- Unconscious adult patients with ROSC after out-of-hospital cardiac arrest (VF) should be cooled to 32°C to 34°C for 12 hours (Class IIa).
- Similar therapy may be beneficial for patients with non- VF arrest out-of or in-hospital arrest (Class IIb).

Various pathophysiological mechanisms are associated to 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 [11]. Neurological injury and mortality after ROSC may be due in part to this “ischemia-reperfusion” injury. The basic concept is that while the lack of blood flow (ischemia) leads to pathophysiological changes, uncontrolled reperfusion (return of blood flow after resuscitation) may amplify these injury

processes. Hypothermia may block a number of these steps and lessen cellular injury by slowing cerebral metabolism in relation with other mechanisms. 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 [12]. It appears that cooling as soon as possible (within several hours of resuscitation) is best, although animal work suggests that cooling during resuscitation might be even better, however this has not been shown clinically at this time [13]. There are no studies comparing early versus delayed hypothermia in humans.

Numerous techniques have been described for inducing mild hypothermia. These embrace ice bags, blankets containing circulating coolant 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 [14]. Infusion of cold (4°C) lactated Ringer solution at 30 mL/kg over 30 minutes after resuscitation from out-of-hospital CA has been a safe and successful cooling technique [15]. This method has been sufficient and effective also in pre-hospital settings, and has also been studied in combination with endovascular cooling or with ice-water cooling blankets [16]. In an animal study, extracorporeal venovenous cooling has been tested as a thriving procedure to rapidly induce therapeutic mild hypothermia [17].

Contraindications to MIH are cardiogenic shock, coagulation disorders, pregnancy, and cardiac arrhythmias. Potential and frequent complications 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 [10]. Myocardial ischemia, infections, and severe rebound hyperthermia may also occur. Therefore it is important that all patients who receive hypothermia should get standard ICU care such as fre-

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 favourable neurological recovery				
HACA	72/136 (53%)	50/137 (36%)	1.5 (1.14-1.89)	0.006
Bernard	21/43 (49%)	9/34 (26%)	1.75 (0.99-2.43)	0.052
Idrissi	4/16 (25%)	1/17 (6%)	4.25 (0.70-53.83)	0.16
Alive at 6 months with favourable neurological recovery				
HACA	72/136 (52%)	50/137 (36%)	1.44 (1.11-1.76)	0.009

quent turning, oral care every 2 to 4 hours, ventilator bundling interventions, glucose level control, peptic ulcer prophylaxis, and deep vein thrombosis prophylaxis [18].

Although, several registries have been founded to follow up the use of MIH after CA and patient outcome (HACA-Registry, Northern Hypothermia network), guideline implementation in every day practice is still poor [18]. Despite recent developments, it remains unclear whether 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 [19]. In a similar survey a year later, the percentage of non-users was 74% in the USA, 69% in Great Britain, and 39% in Finland [20]. Reasons why physicians have not used hypothermia include lack of awareness of supporting data, technical constraints, and the lack of hypothermia protocol incorporation into ALS (Advanced Life Support). Better understanding of the pathophysiology of resuscitation and the injury processes on which hypothermia acts will serve to further promote the use of this promising method to save lives.

Unresolved issues concerning the use of therapeutic hypothermia in CA remain regarding patient selection (children, neonates), optimal timing, duration and depth of cooling, and methods to minimize hypothermia-related complications [21]. Large randomized studies addressing therapeutic hypothermia after out-of-hospital CA with initial rhythms other than VF or in-hospital cardiac arrest have not appeared thus far. Further research is also needed to elucidate the safety and effect of hypothermia in combination with thrombolysis or other neuroprotective methods [22].

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