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Prehospital Therapeutic Hypothermia for Cardiac Arrest

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1. Introduction

In the era before Therapeutic Hypothermia (TH) was recommended and used as a therapeutic modality for out-of-hospital cardiac arrest (OHCA) patients, reported data suggests in-hospital mortality exceeded 58%.^[1,2,3,4,5,6] Mortality after a sudden and unexpected cardiac arrest (CA) is high, and the chance of survival to hospital discharge has, until recently, remained unchanged.^[7] In one report, OHCA in the U.S. has a mortality rate greater than 90% which results in more than 300,000 deaths per year.^[8] Those who survive the devastating event, often retain a hypoxic brain injury and a permanently incapacitating neurologic deficit.^[9] Studies of patients who survived to ICU admission but subsequently died in the hospital, brain injury was the cause of death in 68% after out-of-hospital cardiac arrest and in 23% after in-hospital cardiac arrest.^[10,11]

Recent studies have indicated that TH with a reduction of body core temperature (T) to 33 °C over 12 to 24 hours has improved survival and neurologic outcome in OHCA patients. In 2002, the European Hypothermia after Cardiac Arrest Study Group demonstrated an improvement in survival from witnessed V-fib cardiac arrest from 41% to 55% and an improvement in favorable neurologic outcome among survivors from 39% to 55% when TH of 32-34°C was maintained for the first 24 hours post cardiac arrest.^[12] Bernard demonstrated similar neurologic outcome benefits from 12 hours of TH at 32-34°C induced on the same patient population in Australia.^[13] Recently, a meta-analysis showed that therapeutic hypothermia is associated with a risk ratio of 1.68 (95% CI, 1.29-2.07) favoring a good neurologic outcome when compared with normothermia. The meta-analysis concluded the number needed to treat (NNT) to produce one favorable neurological recovery was 6.^[14] This would translate to improved neurological recovery in > 10,000 patients per year in the U.S.^[14] Also, recent evidence has now shown that the treatment is beneficial in cases with non-VF initial rhythm.^{[15,16,17,18,19].}

Current resuscitation guidelines of the International Liaison Committee on Resuscitation (ILCOR) recommend induction of TH in post-cardiac arrest patients.^[7] In 2005 and then upgraded in 2010, the American Heart Association Advanced Cardiac Life Support Guidelines recommended that “unconscious adult patients with ROSC after out-of-hospital cardiac arrest should be cooled to 32 to 34°C for 12-24 hours....”^[20,21] The guidelines identified the need for cooling to occur in the pre-hospital arena, noting that hypothermia “should probably be initiated as soon as possible after ROSC....”

2. Basic science

A cascade of destructive events and processes begins at the cellular level in the minutes to hours following an initial injury. These processes, the result of ischemia and reperfusion, may continue for hours to many days after the initial injury.^[22]

When hypothermia was first used in a clinical setting it was presumed that its protective effects were due purely to a slowing of cerebral metabolism, leading to reduced glucose and oxygen consumption. Cerebral metabolism decreases by 6% to 10% for each 1°C reduction in body temperature during cooling.^[23,24] This could play a therapeutic effect, but only partially. Therapeutic hypothermia can also effectively inhibit apoptosis.^[25-27] Hypothermia inhibits the early stages of the programmed cell death process.^[26] Thus, inhibiting apoptosis is another mechanism by which therapeutic hypothermia could influence the ischemia reperfusion injury or secondary injury early on in the disease process. Excitatory processes play a major role in the pathophysiology of secondary injury post-cardiac arrest.^[23] Evidence suggests that hypothermia inhibits these harmful excitatory processes occurring in brain cells during ischemia-reperfusion. Ischemic insult to the brain leads to decrease in Adenosine triphosphate (ATP) supplies.^[23] This culminates into an influx of calcium (Ca) into the cell through prolonged glutamate exposure inducing a permanent state of hyperexcitability in the neurons (*excitotoxicity*). All these processes are inhibited by hypothermia very early after injury. Some animal experiments suggest that neuroexcitotoxicity can be blocked or reversed only if the treatment is initiated in the very early stages of the neuroexcitatory cascade.^[28-34] Acute inflammation early after ROSC plays a harmful role in postcardiac arrest, including cytokines, macrophages, neutrophils, and complement activation, leading to free radical formation. Multiple animal experiments and few clinical studies have shown that hypothermia suppresses all these ischemia-induced inflammatory reactions, leading to a significant reduction in free radical formation.^[35-38] Ischemia-reperfusion can also lead to significant disruptions in the blood-brain barrier, which can facilitate the subsequent development of brain edema. Mild hypothermia significantly reduces blood-brain barrier disruptions, and also decreases vascular permeability following ischemia-reperfusion, further decreasing edema formation.^[39-41] The coagulation cascade is also activated with ischemia-reperfusion injury leading to intravascular clot formation resulting in microvascular thrombosis in the brain.^[42,43] Therapeutic Hypothermia could be beneficial in this instance since platelets number and function are decreased with temperatures <35°C, and some inhibition of the coagulation cascade develops at temperatures <33°C.^[44,45] Vasoconstriction, mediated mainly by

thromboxane and endothelin plays a pivotal role in the secondary injury as well. This could also be mitigated by hypothermia ^[46-48]

It is crucial to note that all of these processes after ischemic-reperfusion injury in the brain are temperature dependent; they are all stimulated by fever, and can all be mitigated or blocked by hypothermia. Since most of these processes start within minutes to hours after the injury, then application of hypothermia earlier might be even more beneficial than conventional later application. This has been the premise behind prehospital cooling.

3. Animal studies

Animal studies demonstrate a benefit of very early cooling either during CPR or within 15 minutes of ROSC when cooling is maintained for only a short duration (1 to 2 hours). Equivalent neuroprotection was produced in a rat model of cardiac arrest when a 24-hour period of cooling was either initiated at the time of ROSC or delayed by 1 hour. In a gerbil forebrain ischemia model, sustained neuroprotection was achieved when hypothermia was initiated at 1, 6, or 12 hours after reperfusion and maintained for 48 hours; however, neuroprotection did decrease when the start of therapy was delayed. Mice receiving intra-arrest cooling had more favorable hemodynamic and neurological outcomes compared with normothermic controls with earlier reperfusion time. In another model, Dogs that received hypothermia treatment within 10 minutes of onset of VF had significantly better neurological outcomes than those that received it after 20 minutes of VF. ^[49-53]

4. Human studies

Bernard et al., reported the results of a clinical trial of the rapid infusion of large-volume (30 ml/kg), ice-cold (4°C) lactated ringer's solution in comatose survivors of OHCA. This study found that this approach decreased core temperature by 1.6°C over 25 minutes with no adverse events.^[54] Polderman, et al., used in addition to surface cooling, 30ml/kg (mean 2.3 liters) of cold normal saline over 50 minutes that showed similar results.^[55] Several small randomized trials⁵⁶⁻⁵⁹, and nonrandomized observational and retrospective trials ^[60-66], looked at pre-hospital cooling initiation for patients with OHCA.

The first randomized controlled trial (RCT) of pre-hospital cooling using large volume ice chilled fluid (LVICF) was reported by Kim et al. in 2007. Adult victims of non-traumatic cardiac arrest regardless of the initial rhythm were randomized either to field cooling or conventional treatment. In EMS before hospital arrival, patients assigned to the treatment group were infused up to 2L of 4°C normal saline as soon as possible after resuscitation from out-of-hospital cardiac arrest. A total of 125 patients were randomized to receive standard care with or without intravenous cooling. Among survivors to hospital admission, a significant esophageal temperature decrease of 1.24°C was observed in the treatment group compared to a 0.10°C increase in the control group. The authors report no increase in the number of adverse events associated with field cooling.^[56] Kämäräinen et al conducted a similar safety trial in 2009; patients were cooled using LVICF and compared to patients

Trial	Cooling method	Randomized-controlled	Number of patients	Temperature measurement site	Complications
Kim et al 2007	LVICF	YES	125	esophageal	No difference
Kämäräinen et al 2009	LVICF	YES	37	nasopharyngeal	No difference
Bernard et al 2010	LVICF	YES	234	Tympanic	No difference
Bernard et al 2011	LVICF	YES	163	Tympanic	No difference
Castren et al 2010	Transnasal cooling	YES	200	Tympanic and core	No difference
Callaway et al 2002	Ice Packs	NO	22	Nasopharyngeal	No
Virkkunen et al 2004	LVICF	NO	13	Esophageal	1 hypotension
Uray et al 2008	Cooling pads	NO	15	Esophageal	No
Hammer et al 2009	LVICF	NO	99	Rectal	No difference
Storm et al 2008	Cooling cap	NO	45	Tympanic	No
Kämäräinen et al 2008	LVICF	NO	17	Nasopharyngeal	5 Re-arrests
Bruel et al 2008	LVICF	NO	33	Esophageal	1 Pulmonary edema
Garrett et al 2011	ICF (2000ml)	NO	551	Core	No difference

LVICF; large volume ice chilled fluid, ICF; ice chilled fluid

Table 1. Clinical Trials on prehospital cooling

received conventional fluid therapy. Of 44 patients screened, 19 were cooled using LVICF and 18 patients received conventional fluid therapy. LVICF resulted in a mean decrease in nasopharyngeal temperature of 1.5 °C. At the time of hospital admission, the mean nasopharyngeal temperature was markedly lower in the hypothermia group compared to the control group; 34.1°C vs. 35.2°C, respectively. Otherwise, there were no significant differences between the groups regarding safety parameters.⁵⁷ Bernard et al, in 2010, randomized 234 patients with an initial rhythm of Ventricular fibrillation (VF) to treatment group to receive 2L of LVICF by paramedics or to the control group to be cooled after hospital admission.^[58] Patients allocated to paramedic cooling received a median of 1900 mL of ice-cold fluid. This resulted in a mean decrease in core temperature of 0.8°C. However, patients in both prehospital TH and control groups had equivalent temperatures at 60 minutes after hospital arrival (34.7°C). They did not demonstrate any improvement in survival to hospital discharge among prehospital-cooled patients when compared with

patients receiving TH initiated in the hospital. In a subsequent study, Bernard et al randomized 163 patients with an initial rhythm of non-VF to either pre-hospital cooling using a rapid infusion of LVICF or cooling after hospital admission.^[59] Patients allocated to prehospital cooling received a median of 1500 ml of ice-cold fluid. This resulted in a mean decrease in core temperature of 1.4°C compared with 0.2°C in hospital cooled patients. Although the planned duration of TH in both groups was 24 hours, both groups received a mean of 15 hours cooling in the hospital and only 7 patients in each group were cooled for 24 hours. There was no difference in outcomes at hospital discharge with favorable outcome in the pre-hospital cooled patients, compared with in the hospital cooled patients. In another randomized, controlled trial in 2010, Castren et al examined the use of transnasal cooling in the prehospital setting after ROSC, using an experimental portable delivery device.^[60] They showed that transnasal cooling was safe and effective during arrest, with a rapid onset of TH in the prehospital setting. Although they did not demonstrate a statistically significant difference in survival to hospital discharge, there was a trend to increased survival in the transnasal cooling group compared with the control group (43.8% vs. 31.0%; $p = 0.26$). In a subset of patients who had CPR initiated within 10 minutes of collapse, there was a statistically significant difference in those who survived in the cooled group versus the control group (56.5% vs. 29.4%; $p = 0.04$) and those who were neurologically intact (43.5% vs. 17.6%; $p = 0.03$).

Callaway et al in 2002 applied ice to the heads and necks of 9 patients during CPR, and compared this to a control group of 13 patients.^[61] There was no difference in the rate of cooling in this study. Virkkunen et al, in 2004 reported a feasibility study using post ROSC infusion of 30 ml/kg LVICF after ROSC. In this cohort of thirteen patients, a significant decrease in esophageal temperature was observed, with a mean decrease of 1.9°C compared to the temperature prior to the onset of infusion.^[62] A transient episode of hypotension was observed in one patient, but otherwise the treatment was well tolerated. In 2008, Uray et al used self-adhesive cooling pads to induce cooling in the prehospital setting after ROSC in 15 patients.^[63] The rate of cooling was 3.3 °C/h; the target temperature (33 to 34°C) was reached in hospital after approximately 91 minutes from the time of ROSC. This study also showed that prehospital cooling was feasible and no adverse events were observed. In a retrospective review of 22 patients cooled using LVICF in the prehospital setting following ROSC compared to 77 conventionally treated patients in 2009, Hammer et al showed prehospital cooling to be feasible and safe with a mean cooling rate of -1.7 C/h and no significant increase in the rate of adverse effects in the cooling group compared to the conventional group.^[64] Storm et al, in 2008, studied the feasibility of a cranial cooling cap in the prehospital setting initiated after ROSC in 20 patients compared to 25 patients serving as a non-randomized control group.^[65] A 1.1°C decrease in tympanic temperature was observed in the treatment group. Also, in 2008, Kämäräinen et al enrolled 17 patients in a nonrandomized study where paramedics initiated cooling using LVICF during CPR and after ROSC with a target temperature of 33°C.⁶⁶ The mean infused volume was 1571 ± 517 ml and resulted in a mean admission temperature of 33.83 ± 0.77°C (1.34°C decrease compared to initial nasopharyngeal temperature). There were no major adverse events. In a similar study, Bruel et al enrolled 33 patients out of whom 20 patients had ROSC.⁶⁷ A mean esophageal temperature decrease of 2.1°C was observed. Pulmonary edema occurred in one

patient. No other major adverse events occurred. In 2011, Garrett et al performed a retrospective analysis of individuals experiencing OHCA whereby six months into the study a prehospital intraarrest TH (IATH) protocol was instituted.⁶⁸ In this protocol, patients received 2000 ml of ICF directly after obtaining intravenous access. 551 patients were analysed. Rates of prehospital ROSC were 36.5% versus 26.9% (OR 1.83; 95% CI 1.19–2.81) in patients who received IATH versus normothermic resuscitation respectively. While the frequency of survival to hospital admission and discharge were increased among those receiving IATH, the differences did not reach statistical significance. The secondary analysis found a linear association between the amount of cold saline infused and the likelihood of prehospital ROSC. They concluded that the infusion of 2000 ml of ICF during the intra-arrest period may improve rate of ROSC.

These studies are either underpowered or due to study design do not allow conclusions regarding effects on outcome to be drawn, but the safety and feasibility of early cooling was demonstrated. Another major limitation in most of these studies is that TH is not systematically continued in the post resuscitation care occurring in-hospital. Therefore, it is not possible to evaluate the benefits of pre-hospital cooling alone, as the effect of TH has been shown to necessitate a cooling period of at least 12 to 24 hours.

5. Methods for induction of prehospital therapeutic hypothermia

Most of the trials described above (Table 1) used LVICF for induction of TH in the prehospital setting. All the studies that used LVICF showed that this method for cooling is safe and feasible. However, LVICF may portend some potential problems. In one study on cold fluids, it was shown that chilled fluids begin to warm during transit through intravenous tubing, but the rate was not rapid enough to be deemed potentially clinically significant.⁶⁹ In addition, in some instances, time to transport from the field to the emergency department may be too short for LVICF to have a significant cooling effect. In a study by Spaite et al on prehospital cardiac arrest, the time to transport from the field to the hospital was about 7 minutes.⁷⁰ In the study by Bernard et al above, 52% of the patients did not receive the goal of 2 L chilled saline because the transport time to the hospital was < 20 minutes.⁵⁸ EMS systems with short transport times may not benefit from prehospital TH methods, esp chilled fluids, as much as systems that need longer time to get to their respective facilities. Another cooling method, used by Castren et al was transnasal cooling, with a machine that employs evaporation of an inert liquid sprayed in the posterior nasopharynx.^[60] They did show that this method of transnasal cooling was safe and effective during arrest, with a rapid onset of TH in the prehospital setting. However, it is expensive and not widely available at this point. Another method used was cooling pads by Uray et al.^[63] They used prechilled cooling pads that were stored in an insulated box with a cooling battery. They were able to achieve target temperature within about 50 minutes with only mild dermal erythema, which resolved soon after removal of the pads. Storm et al used cooling caps that proved feasible and with no significant adverse events.^[65] Other promising new technologies include chilled perfluorocarbons and saline/ice “slurries”, that are still at level of animal experimentation.^[71,72]

6. Complications and problems with prehospital therapeutic hypothermia

The usual side effects pertaining to therapeutic hypothermia in general like arrhythmias, electrolyte abnormalities, bleeding, infection and other complications could also happen here, however these are discussed in a previous chapter. In this section, I will discuss the complications and problems pertinent to the prehospital phase of hypothermia induction. Overcooling is a potential problem in the field. It is very important to avoid overcooling below the target range because adverse events likely increase when patients are cooled to $< 32^{\circ}\text{C}$.^[73,74] In a retrospective review, investigators showed that unintentional overcooling below target temperature is common, and concluded that improved mechanisms for temperature control are required to prevent potentially deleterious complications of more profound hypothermia.^[75] I also add that effective and accurate methods for prehospital temperature monitoring is important, such as tympanic or esophageal temperature monitors. Another important complication is shivering, especially in the EMS with some limitations on use of antishivering medications, such as neuromuscular blockers and some sedatives. One important potential problem is the interference of inducing TH in the field with the actual CPR and ACLS ongoing on the patient. Some providers believe that basic resuscitation care should be prioritized over induction of TH, especially with no proven outcome benefit of prehospital TH. A survey of EMS physicians on the implementation rate of prehospital cooling in the United States reported that the most common barriers to prehospital hypothermia are the lack of ideal equipment and space in EMS vehicles to store the equipment that is used to initiate cooling, lack of credentialing for the use of paralytic agents, and difficulty in prioritizing for training and patient care.^[76] Another problem noted from some of the clinical studies addressed above is that after induction of hypothermia in the field, some patients were transported to hospitals where TH is not systematically continued in the post resuscitation care occurring in-hospital. If a patient is cooled only to be rewarmed soon after transport to a facility, then this may actually be worse than not cooling the patient to begin with, as this might reverse and maybe even cause a rebound in all of the mechanisms of secondary injury (ischemia-reperfusion) discussed above. Hence, it is very important that these patients be transported to a facility staffed and equipped with the ability to continue in-hospital therapeutic hypothermia for at least 12-24 hours in addition to the other bundles of resuscitative care.^[7]

7. Conclusion

Animal and laboratory data have suggested that there is significantly decreased neurological injury if cooling is initiated as soon as possible after resuscitation. Human clinical studies are either underpowered or due to study design do not allow conclusions regarding effects on outcome to be drawn, but the safety and feasibility of early cooling was strongly demonstrated. Prehospital cooling comes with its own logistic challenges, such as limitation of EMS vehicle space, lack of ideal equipment for induction of hypothermia and for temperature monitoring, lack of credentialing for use of paralytic agents by EMS teams

that are not staffed by physicians, transport to facilities that are not equipped to continue in-hospital therapeutic hypothermia and postresuscitation care, the potential for overcooling and shivering, and interference with basic resuscitation efforts in the field. Intra-arrest and post-arrest bundles of care that include therapeutic hypothermia, as well as training of EMS teams, EMS physicians, emergency room staff, cardiologists and cardiac catheterization lab staff, and intensive care unit physicians and staff on these protocols and bundles are crucial for the success of these bundles and the implementation of this important therapy, whether cooling is initiated in the field or in the hospital setting. Clearly, large prospective randomized controlled trials of prehospital therapeutic hypothermia preferably as part of a cardiac arrest bundle of care are needed.

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The author reports no conflicts of interest.

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